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Amisulpride: Efficacy and Adverse Events in the Management of Postoperative Nausea and Vomiting — a Systematic Review and Quantitative Meta-analysis

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Abbreviations

5-HT3	5-hydroxytryptamine
AE	Adverse Event
CI	Confidence Interval
CINV	Chemotherapy-Induced Nausea and Vomiting
CPG	Central Pattern Generator
FDA	Food and Drug Administration
IM	intramuscular
IV	intravenous
mg	miligram
ms	millisecond
NTS	Nucleus tractus solitaries
PO	per os
PONV	Postoperative Nausea and Vomiting
RR	Relative Risk
SAE	Severe Adverse Event
TEAE	Treatment-Emergent Adverse Event

1. Introduction

1.1 *Definitions*

Nausea is a subjective unpleasant sensation, associated with an urge to vomit.

Vomiting is a forceful expulsion of gastric contents through the mouth, which involves elevation of the soft palate, relaxation of pharyngeal muscles, descent of diaphragm as well as contractions of the abdominal and respiratory chest muscles.

Retching, which usually comes before vomiting, is associated with activation of the same muscles, however without expulsion of any stomach contents (Andrews 1992; Apfel et al. 2002).

Postoperative Nausea and Vomiting (PONV) is often defined as any nausea and/or retching/vomiting 24-28h after surgery (Pierre and Whelan 2013). For the studies on PONV Apfel et al. recommend to limit the observation period to 24 h. Additionally PONV can be classified into early (0-2h) and delayed (2-24h) PONV (Apfel et al. 2002).

1.2 *Postoperative Nausea and Vomiting*

Despite the advances in anesthesiology, postoperative nausea and vomiting (PONV) with its complex aetiology still remains a common postoperative complication among many patients.

PONV occurs in 20-30% of all surgical patients when balanced anaesthesia techniques are used without pharmacological prophylaxis and in up to 80% of the patients with multiple risk factors (Gan et. al 2014, Watcha and White 1992). Even though PONV is often considered a big “little” problem (Kapur 1991), it may lead to severe complications including dehydration, electrolyte imbalances, aspiration pneumonia, oesophageal rupture, wound dehiscence, subcutaneous emphysema, pneumothorax and loss of vision (Apfel et al. 2012). PONV is undoubtedly a distressing complication for patients, leading to dissatisfaction associated with general anaesthesia (Eberhart et al. 2002). Moreover, it poses an economic burden due to a protracted stay in the recovery room after operation, delays in discharge, additional antiemetic medication and nursing time as well as readmission to the hospital after ambulatory surgery (Hirsch 1994).

Several studies investigating which risk factors could be independent predictors of PONV showed that it is associated with patient-specific (female gender, nonsmoking status, history of PONV and/or motion sickness, younger age) or anaesthesia-related (use of volatile anaesthetics and/or nitrous oxide, postoperative opioid use, duration of anaesthesia) risk factors. While female gender is the strongest patient specific risk factor, the use of volatile anaesthetics is the strongest anaesthesia-related predictor for PONV. Certain types of surgery such as bariatric, gynecological, laparoscopic surgery and cholecystectomy may be linked to an increased risk of PONV (Gan et al. 2020). With development of the simplified risk scores, such as Apfel score (female gender, history of PONV and/or motion sickness, nonsmoking and postoperative opioid use) and Koivuranta's score (female gender, history of PONV and/or motion sickness, nonsmoking and duration of surgery), which have been most widely used to assess patient's individual risk of PONV, more attention has been drawn to the problem of PONV in clinical practice (Apfel et al. 1999, Apfel et al. 2012, Koivuranta et al. 1997).

The incidence of PONV in patients with none, one, two, three or four Apfel score risk factors is 10%, 21%, 39%, 61%, 79% respectively (Apfel et al. 1999). Current guidelines recommend baseline risk assessment for PONV through a validated risk score. Patients with one or more risk factors for PONV should be identified early and a multimodal management consisting of both pharmacological and non-pharmacological (baseline risk reduction) strategies should be adopted. A decrease in the baseline risk can be achieved through several means. These include avoiding general anaesthesia in favor of a regional one when possible, use of propofol and avoidance of volatile anaesthetics and nitrous oxide, adequate hydration, reduction in intraoperative and postoperative opioid use and substituting neostigmine with suggammadex for the reversal of neuromuscular blockade (Gan et al. 2020).

1.3 *Pathophysiology*

Mechanisms underlying PONV are very complex and so far not fully understood. While vomiting is an autonomic reflex, nausea requires conscious perception involving cerebral cortex (Apfel 2005).

The main area responsible for coordinating vomiting, a so-called vomiting centre, is located within the brain stem in the medulla oblongata (Andrews 1992). However, since the exact location of the neurons integrating afferent information and producing an efferent response resulting in emesis is not known, recently the concept of a central pattern generator (CPG), activating neurons in a proper sequence, has been favored. Nucleus tractus solitarius (NTS),

some nuclei in the area of the reticular formation, as well as the respiratory nuclear groups, are believed to act as command neurons that activate CPG to generate an emetic response (Horn et al. 2014).

Four main pathways activating vomiting through direct projections to the nucleus tractus solitarii (NTS) can be distinguished, namely the vagal afferent fibres of the gastrointestinal tract, the vestibular labyrinth system in the inner ear, the forebrain and the area postrema (Horn et al. 2014).

Toxic stimuli or drugs lead to a release in serotonin from the enterochromaffin cells of the gastrointestinal tract, which then binds to the 5-hydroxytryptamine (5-HT3) receptors and stimulates vagal afferent neurons (Gan 2007). The vestibular system receives stimuli that trigger motion sickness, while the forebrain is associated with both ictal vomiting (through activation of the insular cortex and temporal lobe, including the amygdala) as well as seizures and psychogenic vomiting (Horn et al. 2014). Located in the area postrema on the floor of the fourth ventricle, the Chemoreceptor trigger zone (CTZ) lacks a blood-brain barrier, which allows it to detect emetic drugs and toxins both in the blood and in the cerebrospinal fluid (Gan 2007, Apfel 2005). CTZ not only contains receptors for neurotransmitters such as serotonin, dopamine, histamine, acetylcholine and neurokinin, which are the targets of modern antiemetics, but also μ-opioid receptors which can explain the opioid induced emesis (Gan 2007). Furthermore, peripheral effects of opioids as well as inhalational anaesthetics induce disruption of gastrointestinal function, additionally contributing to postoperative nausea and vomiting (Horn et al.2014).

1.4 *Pharmacological prophylaxis and treatment*

1.4.1 Overview

According to the most recent Fourth Consensus Guidelines for the management of postoperative nausea and vomiting, published in 2020, multimodal pharmacological prophylaxis is advised for patients with one or more risk factors for PONV, being one of the major changes in the management of PONV since the 2014 Guidelines (Gan et al. 2020).

The main classes of antiemetic drugs include 5-hydroxytryptamine (5-HT3) receptor antagonists (granisetron, ondansetron), corticosteroids (dexamethasone), neurokinin-1 (NK-1) receptor antagonists (aprepitant, fosaprepitant), anticholinergics (scopolamine), antihistamines (meclizine, dimenhydrinate) as well as dopamine D2 receptor antagonists (haloperidol,

droperidol) (Gan et al. 2020). Generally, each of those classes shows similar efficacy in reducing the absolute risk of PONV by 25%, combining different antiemetic drug classes has an additive effect in PONV risk reduction (Gan et al. 2014).

The main classes of antiemetic drugs, their receptor affinities, doses, time and route of administration are listed in the Table 1 (Watcha and White 1992, Gan, 2020).

Table 1. *Main classes of antiemetic drugs (Adapted from Watcha and White 1992, Gan, 2020).*

Antiemetic group	Receptor affinity					Dosis and dry administration	Time of administration
	D_2	M_1	Histamine	$5HT_3$	NK_1		
Corticosteroids							
Dexamethasone	–	–	–	–	–	4-8 mg *iv*	At induction
Methylprednisolone						40 mg *iv*	
5-Hydroxytryptamine receptor antagonists							
Granisetron						0,35-3 mg *iv*	
Ondansetron	–	–	–	++++	–	4 mg *iv,* 8 mg *PO*	End of surgery
Palonsetron						0,075 mg *iv*	
Tropisetron						2 mg *iv*	
Dolasetron						12,5 mg *iv*	
Ramosetron							
Antihistamines							
Dimenhydrinate	+	++	++++	–	–	1 mg/kgbw *iv*	End of surgery
Promethazine	++	++	++++	–	–	6,25 mg	
Neurokinin-1 receptor antagonists							
Aprepitant					++++	40 mg PO	At induction
Casopitant						150 mg *PO*	
Rolapitant						70-200 mg *PO*	
Anticholinergics							
Scopolamine	+	++++	+	–	–	1 mg/24h (*trans-dermal patch*)	Prior evening or 2 hours before surgery
Antidopaminergics							
Amisulpride	++++	–	–	–	–	5 mg *iv*	At induction
Metoclopramide	+++	–	+	++	–	10 mg *iv*	-
Droperidol	++++	–	+	+	–	0,625 mg *iv*	End of surgery
Haloperidol	++++	–	+	–	–	0,5-2 mg *iv/im*	-
Perphenazine	++++	no data	no data	no data	–	5 mg *iv*	-

1.4.2 Corticosteroids

The most commonly used and best-studied corticosteroid for the management of PONV is dexamethasone. Dexamethasone's mechanism of action is complex and not yet fully known. One can speculate on its anti-inflammatory potential, resulting in a decrease in arachidonic acid and the release of inflammatory mediators release with subsequent nerve sensitization to neurotransmitters involved in the emesis could be responsible for its antiemetic properties. Apart from the central effects in the NTS, it may also directly inhibit the 5-HT_3 receptors (Horn et al. 2014). Moreover, a single iv dexamethasone dose reduces postoperative pain and need for opioid use, which might also contribute to its antiemetic potential (Waldron et al. 2013, Gan et al. 2020). Current Guidelines recommend a 4-10 mg prophylactic dose of dexamethasone administered intravenously at the beginning of the surgery (Gan et al. 2020). Even though long-term steroid treatment is associated with severe side effects, such as hypertension, diabetes, osteoporosis, increased infection risk and adrenal insufficiency, adverse effects of a single antiemetic dose are rarely reported. A recent Cochrane meta-analysis found that dexamethasone doesn't contribute to postoperative wound infection and the increase in glucose levels observed after intravenous injection is mild even in patients with diabetes (Polderman et al.2018, Gan et al. 2020). Other corticosteroids, such as methylprednisolone appear to have a comparable efficacy to dexamethasone in PONV reduction and also show opioid-sparing effects (Gan et al. 2020). Low cost and good safety profile make dexamethasone an attractive first-line antiemetic (Apfel et al. 2004).

1.4.3 5-hydroxytryptamine (5-HT_3) receptor antagonists

5-HT_3 receptor antagonists constitute one of the most the most widely used antiemetics, both for prophylaxis and treatment of PONV. Their mechanism of action most likely involves 5-HT3 receptor antagonism both centrally in the area postrema as well as peripherally in the vagal afferents located in the gut (Horn et al. 2014).

Ondansetron, considered the "gold standard" in PONV prevention and therapy, is the most frequently used and best-studied representative of this pharmacological group (Gan et al. 2020). Its efficacy was shown to be similar to dexamethasone 4 mg, droperidol 1,25 mg, while granisetron 1-3 mg IV, ramosetron 0.3 mg IV, palonosetron 0.075 mg, fosaprepitant 150 mg IV and aprepitant 80 mg PO were superior to ondansetron in the management of PONV (Apfel et al. 2004, Gan et al. 2020).

Dolasetron, a highly selective 5-HT_3 receptor antagonist, is recommended by the current guidelines in a 15,5 mg IV dose at the end of anaesthesia with efficacy similar to that of ondansetron. In 2010 the FDA banned the use of dolasetron for Chemotherapy-Induced Nausea and Vomiting (CINV) due to the risk of QT prolongation and severe cardiac arrhythmias, however its use in PONV, where lower doses are administered, was not contraindicated (FDA Drug Safety Communication 2010).

Granisetron exerts similar efficacy to the first generation of 5-HT_3 receptor antagonists as well as dexamethasone 8 mg and its use is recommended in the 0.35-

3 mg dose range at the end of surgery (Gan et al. 2020).

Tropisetron, a highly competitive and selective representant of this group found its antiemetic use mostly in the CINV treatment. A 2 mg IV dose at the end of surgery is recommended for preventing PONV. Tropisetron is not approved in the USA, but still used in Asia and Europe (Gan et al. 2020).

Ramosetron, also not approved in the USA, was found to be effective at a 0.3 mg IV dose.

Palonosetron, introduced to the market in 2003, is a longer-acting, second generation serotonin antagonist with plasma half-life of 40 h (Horn et al. 2014, Rojas et al. 2014). Palonosetron 0.075 mg was shown to be more effective than the aforementioned 5-HT_3 antagonists with an efficacy that is comparable to aprepitant 40 mg PO (Gan et al. 2020).

1.4.4 Antihistamines

Even though H_1 receptor antagonists such as dimenhydrinate have been used as antiemetics for many years, this class of agents is not well studied with the optimal dosing, time of administration and safety profile still remaining unclear (Kranke et al. 2002). Also data on promethazine for PONV prevention is very limited, with guidelines recommending a 6.25 mg dose. Notably, promethazine also carries a black-box warning for its risk of serious tissue damage when administered incorrectly and the FDA recommends a deep intramuscular injection as the preferred route of administration (Gan et al.2020).

1.4.5 Neurokinin-1 receptor antagonists

NK-1 receptor antagonists, a relatively new antiemetic class, act mostly in the NTS and the areas of reticular formation by blocking NK-1 receptors involved in the emetic reflex (Horn et al. 2014).

Aprepitant, available both in oral as well as parenteral (fosaprepitant) form, was shown to reduce emesis rather than nausea. Both aprepitant 40 mg IV and fosaprepitant 150 mg IV are more efficacious against PONV than ondansetron (Gan et al. 2020). Several other NK-1 receptor antagonists, developed for controlling PONV, such as casopitant and rolapitant have not yet been approved for this indication (Liu et al.2015, Gan et al. 2020).

1.4.6 Anticholinergics

Scopolamine acts as a nonselective post-ganglionic muscarinic receptor antagonist and directly inhibits the transmission of cholinergic impulses in the vestibular nuclei (Horn et al. 2014). Transdermal scopolamine patch was shown to be effective in PONV prevention up to 24 hours after surgery with mild side effects including visual disturbances, dizziness and dry mouth (Apfel et al. 2010, Gan et al. 2020). Due to the late onset of effect, current guidelines recommend applying the patch the night before surgery or 2-4 hours before (Gan et al. 2020).

1.4.7 Dopamine antagonists

1.4.7.1 Overview

Dopamin D_2 and D_3 receptors play an important role in nausea and vomiting, most probably by inhibiting the adenylate cyclase, with a consequent increase of cAMP in neurons located in the area postrema and the nucleus tractus solitarii. Competitive antagonism of these receptors is responsible for antiemetic properties of drug classes, such as phenotiazines (promethazine, chlorpromazine, perphenazine), benzamides (metoclopramide) and butyrophenones (droperidol and haloperidol) (Horn et al. 2014, Gan 2007).

1.4.7.2 Phenotiazines

Chlorpromazine and promethazine have been used in the past to treat PONV, however frequent adverse events including sedation and lethargy as well as lack of much evidence of their effect have limited their use (Gan 2007, Gan et al. 2014). Perphenazine at 5 mg dose has been shown to be effective in PONV prevention without the typical side effects of older phenotiazines (Schnabel et al. 2010).

1.4.7.3 Metoclopramide

Metoclopramide acts on D_2, H_1 and 5-HT_3 receptors and shows additional prokinetic properties in the gastrointestinal tract through D_2 antagonism and 5-HT_4 agonism (Horn et al. 2014). Even though metoclopramide has been widely used for many years, it's clinical efficacy at preventing PONV is not certain (Gan et al. 2020). A 10 mg iv prophylactic dose was shown to be effective at preventing PONV and is recommended in current guidelines (De Oliveira Jr et al. 2012, Gat at al. 2020). A multicenter trial of 10, 25 and 50 mg metoclopramide in combination with 8 mg dexamethasone found that only 25 mg and 50 mg doses, administered 30-60 min before the end of the operation, significantly reduced the incidence of PONV. However, the incidence of adverse events, such as tachycardia, hypotension and extrapyramidal disorders increased with increase in the drug's dose. Therefore, a combination therapy with metoclopramide is not recommended (Wallenborn et al. 2006, Gan et al.2020).

1.4.7.4 Haloperidol

Haloperidol, a potent D_2 antagonist, frequently used for the treatment of psychosis and agitation, has been shown to be effective at low doses (0.5-2 mg IM/IV) for the management of PONV. In this dosage, typical adverse effects, such as extrapyramidal symptoms or sedation were rare and no cardiac arrhythmias were reported (Buettner et al. 2004, Gan et al. 2020). Haloperidol carries a QTc prolongation risk in its label and its intravenous use as well as its use as an antiemetic is not FDA-approved (Gan et al. 2014, Gan et al. 2020).

1.4.7.5 Droperidol

The Dopamine D_2-antagonist droperidol was a commonly used and cost-effective antiemetic up until 2001, when it received a black-box warning from the US Food and Drug Administration (FDA). Black-box warning highlights severe and life-threatening adverse reactions and consequently, provides advice about precautions and drug use restrictions in order to prevent serious adverse events (FDA. Guidance for Industry 2011). The warning on droperidol was based on cases of QTc interval prolongation (values ≥390 ms in men and ≥460 ms in women) resulting in severe cardiac arrhythmias, such as torsade de pointes when used in doses >25 mg (Gan et al. 2020, McKeage et al. 2006, Rautaharju et al. 2009). Even though at low doses (0.625 to 1.25 mg IV) it has been shown to be safe and effective at preventing PONV, droperidol is no longer a first-line antiemetic agent in many countries (Gan et al. 2020, Habib

and Gan 2008). Consequently, research on alternative agents blocking the dopamine receptor has recently been intensified.

1.4.7.6 Amisulpride

1.4.7.6.1 Overview

Amisulpride (Solian ®), a substituted benzamide derivate has been on the market for over thirty years. The drug was first introduced in France and found its therapeutic use in the treatment of both positive and negative symptoms of schizophrenia in over 50 countries worldwide. Additionally, in Italy, it is also used for the treatment of dysthymia (Coulouvrat and Dondey-Nouvel 1999, Pani and Gessa 2002, Solian Product Information 2006). The recommended daily oral doses range from 50-800 mg/day and in individual cases can be increased up to 1200 mg/day (Solian Product Information 2006).

1.4.7.6.2 Pharmacodynamics

Amisulpride shows high selectivity for dopamine D_2 (K_i = 2.8 nM), D_3 (K_i = 3.2 nM) as well as 5-HT_{7a} serotonin receptors with low affinity to other serotonin and dopamine receptor subtypes as well as histamine, adrenergic and cholinergic receptors. Low doses preferentially inhibit presynaptic dopamine receptors, enhancing dopamine transmission, while high doses block postsynaptic dopamine receptors, inhibiting the dopaminergic activity in the limbic system (Abbas et al. 2009, Schoemaker et al.1997).

1.4.7.6.3 Pharmacokinetics and metabolism

After oral route of administration amisulpride undergoes rapid biphasic absorption with first plasma peak concentration at 1h (C_{max} = 42.3 ± 3.3 ng/ml) with subsequent one at 3 to 4 hours (C_{max} = 55.7 ± 3.7 ng/ml). Amisulpride shows extensive volume of distribution of 5,8 l/kg, minimal hepatic metabolism and is primarily excreted in an unchanged form via the renal (22–25% after oral, 50% after IV administration) and faecal route (Fox et al. 2019, Rosenzweig et al. 2002). The terminal plasma elimination half-life ($t_{½}$) is about 7–8 hours after intravenous and 12 hours after oral administration. Renal clearance (17–20 l/h, 330 ml/min) is decreased in patients with renal failure, therefore, in these patients the dose should be adjusted based on the degree of renal impairment. In elderly patients, no dose modification is necessary due to

amisulpride's safe pharmacokinetic profile in the geriatric population (Solian Product Information 2006, Curran and Perry 2001). Minimal metabolism, low rate of plasma protein binding (17%) and no inhibition of the cytochrome CYP 450 isoenzymes contribute to amisulpride's low risk for drug interactions (Gillet et al. 2000).

1.5 *Aim of the study*

In 2010, a repurposed formula of amisulpride for intravenous injection was patented and since then various clinical trials were started to study its antiemetic potential in the management of PONV (Smyla et al. 2020).

The purpose of this meta-analysis was to evaluate the efficacy and safety of intravenous amisulpride on both prevention and treatment of PONV from the clinical data available so far.

2. Materials and Methods

2.1 *Clinical Studies Investigator*

From February 2016 until September 2016, I was a clinical investigator responsible for patient recruitment in two multicenter Phase III Studies, which looked at the effects of intravenous amisulpride on treatment of established PONV, later published by Candiotti et al. 2019 and Habib et al. 2019. Both trials were conducted in accordance with the specifications of drug regulatory agencies to gain approval for a new drug.

2.2 *Search strategy and study selection*

A systematic review (meta-analysis) was conducted according to the 2009 PRISMA guidelines. Two independent investigators searched MEDLINE (PubMed), ClinicalTrials.gov and Cochrane Controlled Register of Trials (CENTRAL) databases for randomized, controlled trials on intravenous amisulpride. No language or publication year restrictions were applied. Studies wherein the intervention groups receiving intravenous amisulpride for prophylaxis or treatment of PONV when compared to placebo or another antiemetic were included in the meta-analysis. Keywords used in the search included “sultopride", "amisulpride", "postoperative nausea and vomiting", “ponv”, "nausea” and "vomiting". Exclusion criteria included non-randomised trials, animal studies or review articles (Smyla et al.2019).

2.3 *Data extraction*

Two independent investigators (Natalia Smyla and Prof. Leopold Eberhart) selected studies, extracted data as well as assessed the risk of bias. A modified Cochrane data collection form was used for data extraction. For duplicate removal and reference management Mendeley Version 1.19.2 was used. Disagreements were resolved by reaching a consensus with a third investigator (Dr. Stefanie Weibel and/or Prof. Peter Kranke). The risk of bias was assessed using the Cochrane Collaboration’s tool (Smyla et al. 2019).

2.4 *Primary and secondary endpoints*

The primary endpoint of the study was the incidence of PONV (any episode of retching/vomiting or use of rescue medication) 24-hours postoperatively or 24-hours after IV amisulpride administration. Rescue medication use 24 hours after operation or study drug administration and the incidence of the most frequent treatment-emergent adverse events (TEAEs) were secondary endpoints of the study (Smyla et al. 2019).

2.5 *Statistical analysis and risk of bias assessment*

A random-effects model meta-analysis was carried out in ReviewManager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Results were calculated using the Mantel-Haenszel Method and presented as relative risk (RR) with 95% confidence interval (CI). The χ-square test and I^2 statistic were used to measure heterogeneity. For all outcomes, differences were considered significant at *P* values < 0.05. A subgroup analysis was carried out for different doses of IV amisulpride. Forest plots were created to illustrate the results. Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (Smyla et al. 2019).

3. Results

3.1 *Study Selection*

The database search performed in February 2019 revealed altogether fourteen publications. Among these, seven were removed as they constituted duplicates and two studies were excluded after screening their titles and abstracts. Finally, five randomised, placebo-controlled studies (n= 3313) were assessed as eligible and included in the meta-analysis (Smyla et al. 2019) (Figure 1).

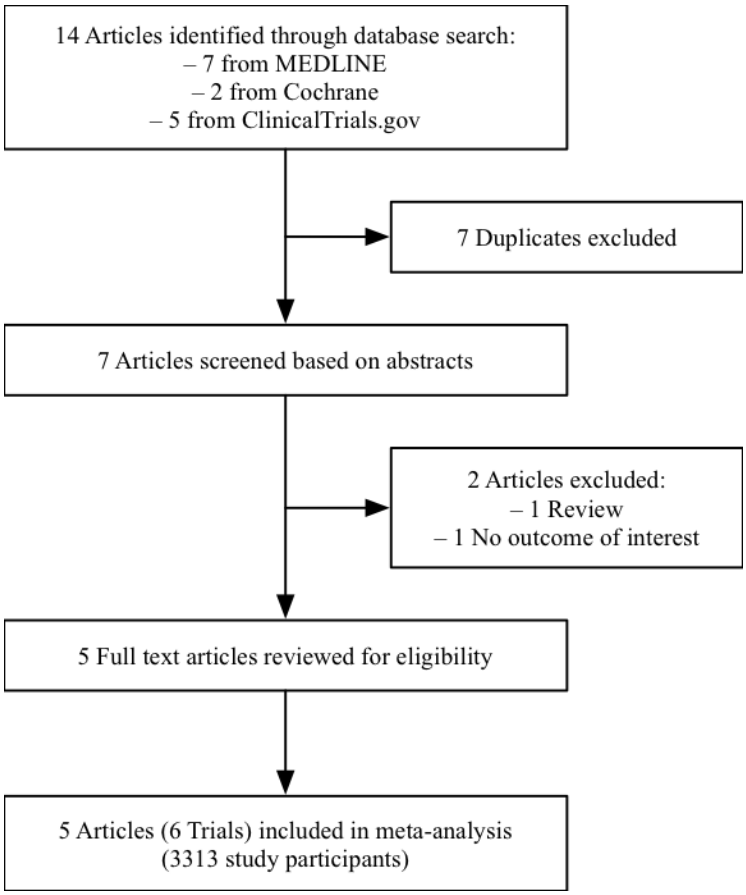

Figure 1. *Flow chart of the literature search and study selection process. Adapted from Smyla et al. 2019.*

3.2 *Study characteristics*

The five analysed studies were issued between 2013 and 2019 (Kranke et al. 2013, Gan et al. 2017, Kranke et al. 2018, Habib et al. 2019, Candiotti et al.2019). The Gan et al. study

included two identical trials conducted in the USA and Europe and therefore, the pooled results of those trials were used for the meta-analysis.

Three trials investigated amisulpride for the prophylaxis of postoperative nausea and vomiting; two of these tested amisulpride as monoprophylaxis, whereas one of the trials added one antiemetic with amisulpride or placebo.

The remaining two studies analysed amisulpride versus placebo in the treatment of PONV (Candiotti et al. - in patients not receiving any prophylaxis and Habib et al. in patients who have been administered up to three prophylactic antiemetics).

The characteristics of the five included studies such as number of patients, the percentage of female participants, baseline risk of PONV, anaesthesia type and prior PONV prophylaxis are showed in Table 2.

Table 2. *Characteristics of included studies (Adapted and modified from Smyla et al. 2019).*

		Habib 2019			Candiotti 2019			Kranke 2018		Gan 2016		Kranke 2013			
		Amisulpride 5 mg	Amisulpride 10 mg	Placebo	Amisulpride 5 mg	Amisulpride 10 mg	Placebo	Amisulpride 5 mg	Placebo	Amisulpride 5 mg	Placebo	Amisulpride 5 mg	Amisulpride 10 mg	Amisulpride 20 mg	Placebo
Number od subjects (n)		237	230	235	191	188	181	572	575	315	311	58	50	53	54
Sex, female %		213 (89.9%)	208 (90.4%)	212 (90.2%)	146 (76.4%)	145 (77.1%)	136 (75.1%)	552 (96.5%)	557 (96.9%)	75%	78%	91%	96%	92%	87%
History of PONV		123 (51.9%)	110 (47.8%)	121 (51.5%)	7 (3.7%)	14 (7.7%)	10 (5.2%)	227 (39.7%)	225 (39.1%)	131 (41.6%)	113 (36.3%)	21 (39%)	21 (36%)	20 (40%)	47 (87%)
Non-smoker		183 (77.2%)	161 (70%)	166 (70.6%)	121 (64.4%)	96 (53%)	119 (62.3%)	516 (90.2)	514 (89.4%)	261 (82.9%)	262 (84.2%)	37 (85%)	42 (84%)	40 (75%)	46 (85%)
Postoperative Opiod Use		No data			No data			567 (99.1%)	573 (99.7%)	307 (97.5%)	301 (96.8%)	39 (67%)	31 (62%)	37 (70%)	33 (61%)
PONV Risk Profile		Moderate-to-high risk			Low-to-moderate Risk of PONV			3-4 Apfel score Risk Factors		≥2 Apfel score Risk Factors		≥2 Apfel score Risk Factors			
2 risk factors		17 (7.2%)	10 (4.3%)	7 (3.0%)	66 (35.1%)	66 (36.5%)	70 (36.6%)	1 (0.2%)	1 (0.2%)	88 (27.9%)	89 (28.6%)	24 (41%)	14 (28%)	19 (36%)	16 (30%)
3 risk factors		90 (38%)	108 (47%)	105 (44.7%)	105 (55.9%)	90 (49.7%)	99 (51.8%)	321 (56.1%)	326 (56.7%)	149 (47.3%)	148 (47.6%)	22 (38%)	20 (40%)	22 (42%)	23 (43%)
4 risk factors		129 (54.4%)	111 (48.3%)	121 (51.5%)	7 (3.7%)	9 (5.0%)	12 (6.3%)	250 (43.7%)	248 (43.1%)	78 (24.8%)	74 (23.8%)	12 (21%)	16 (32%)	12 (23%)	15 (28%)
PONV Prophylaxis		1-3 Standard nondopaminergic Antiemetic, most commonly Ondansetron, Dexamethason, Granisetron or Scopolamine			None			One Standard nondopaminergic Antiemetic, most commonly Ondansetron, Dexamethason or Betamethasone		None		None			
Type of surgery	**Open technique**	108 (45.6%)	98 (42.6%)	121 (51.5%)	79 (41.4%)	81 (43.1%)	74 (40.9%)	273 (47.5%)	281 (49.1%)	186 (59%)	194 (62.4%)	69% overall abdominal surgery, 24% breast or axillary surgery; laparoscopic technique was used in 25% of patients			
	Laparoscopic	129 (54.4%)	132 (57.4%)	114 (48.5%)	112 (58.6%)	107 (56.9%)	107 (59.1%)	302 (52.5%)	291 (50.9%)	120 (38.1%)	115 (37%)				
Type of Anaesthesia		General inhalational anaesthesia													

3.3 *Primary Endpoints*

Three studies tested intravenous amisulpride (Kranke et al. 2013 1, 5 and 20 mg doses; Gan etl al. and Kranke et al 2018 5 mg) in the prevention of postoperative nausea and vomiting 24-hours after surgery. PONV was defined as any retching/vomiting (emesis) or the use of rescue medication. The secondary endpoint included the incidence of nausea.

Two studies examined 5 and 10 mg amisulpride doses for the treatment of established PONV (episode of retching/vomiting or nausea up to 24 hours postoperatively, for which patients requested antiemetic medication).

Both trials then evaluated the incidence of PONV, defined as an emetic episode or the use of rescue medication from 30 minutes to 24 hours postoperatively.

Figure 2 shows the efficacy of 1, 5 and 20 mg intravenous amisulpride on PONV prophylaxis 24 hours after surgery. The pooled effect estimate of all trials revealed a significant decrease in the incidence of PONV (RR = 0.78; 95% CI, 0.72–0.85, $p < 0.00001$) in patients receiving amisulpride as compared to placebo. Subgroup analysis according to the administered dose showed that only doses of 1 and 5 mg and not 20 mg amisulpride significantly reduced the risk of PONV.

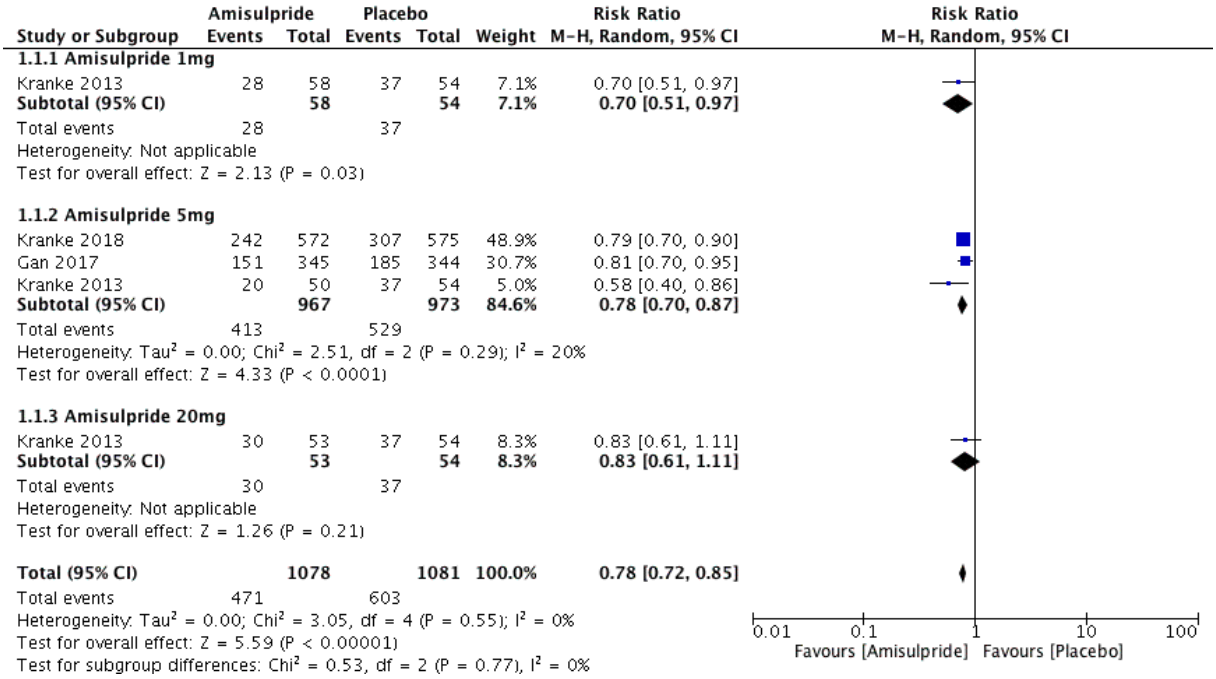

Figure 2. *Forest plot showing the effect of intravenous amisulpride for PONV prophylaxis 24 hours postoperatively. This figure was adapted from (Smyla el al. 2019).*

Figure 3 shows the effect of 5 and 10 mg intravenous amisulpride dose 24 hours after administration. Both 5 mg (RR = 0.9; 95% CI, 0.83–0.98; p = 0.02) and 10 mg amisulpride doses (RR = 0.85; 95% CI, 0.77–0.93; p = 0.0004) significantly reduced the incidence of PONV with overall RR of 0.87 (95% CI; 0.82–0.93, p < 0.0001).

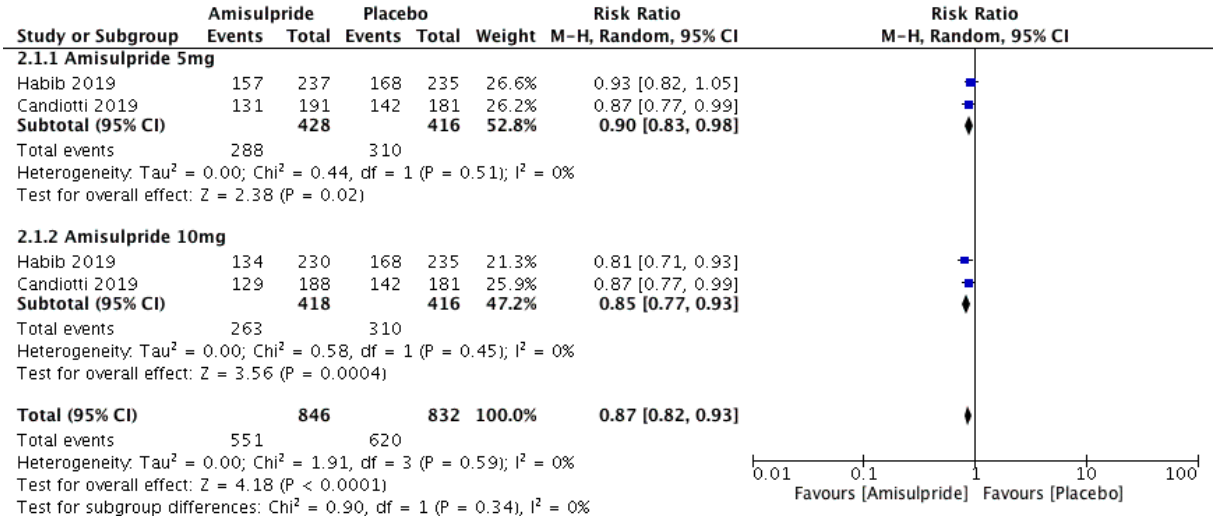

Figure 3. *Forest plot showing the effect of intravenous amisulpride for PONV treatment 24 hours after administration. This figure was adapted and modified from (Smyla el al. 2019).*

3.4 *Secondary Endpoints*

3.4.1 Use of rescue medication

Figure 4 shows the rescue medication use 24 hours after surgery or study drug administration. Amisulpride significantly decreased the use of rescue medication as compared to placebo (RR = 0.83; 95% CI, 0.78–0.88, p < 0.00001) (Smyla et al. 2019).

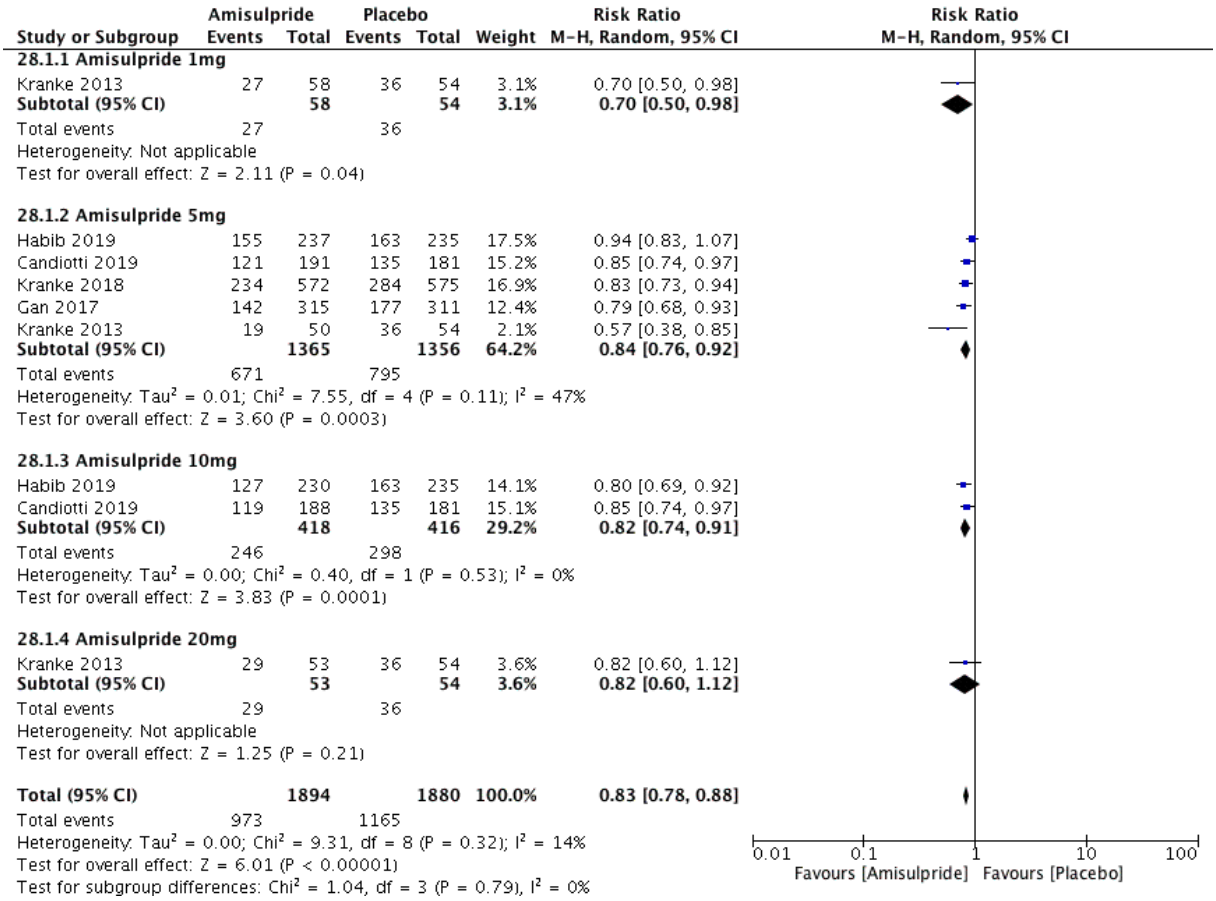

Figure 4. *Forest plot showing the rescue medication use 24 hours postoperatively or after study drug administration. This figure was adapted and modified from (Smyla el al. 2019).*

3.4.2 Treatment Emergent Adverse Events (TEAE)

The incidence of reported TEAE was significantly lower in the amisulpride group as compared to placebo (RR= 0.9; 95% CI, 0.84–0.96, p=0.0008) (Figure 5).

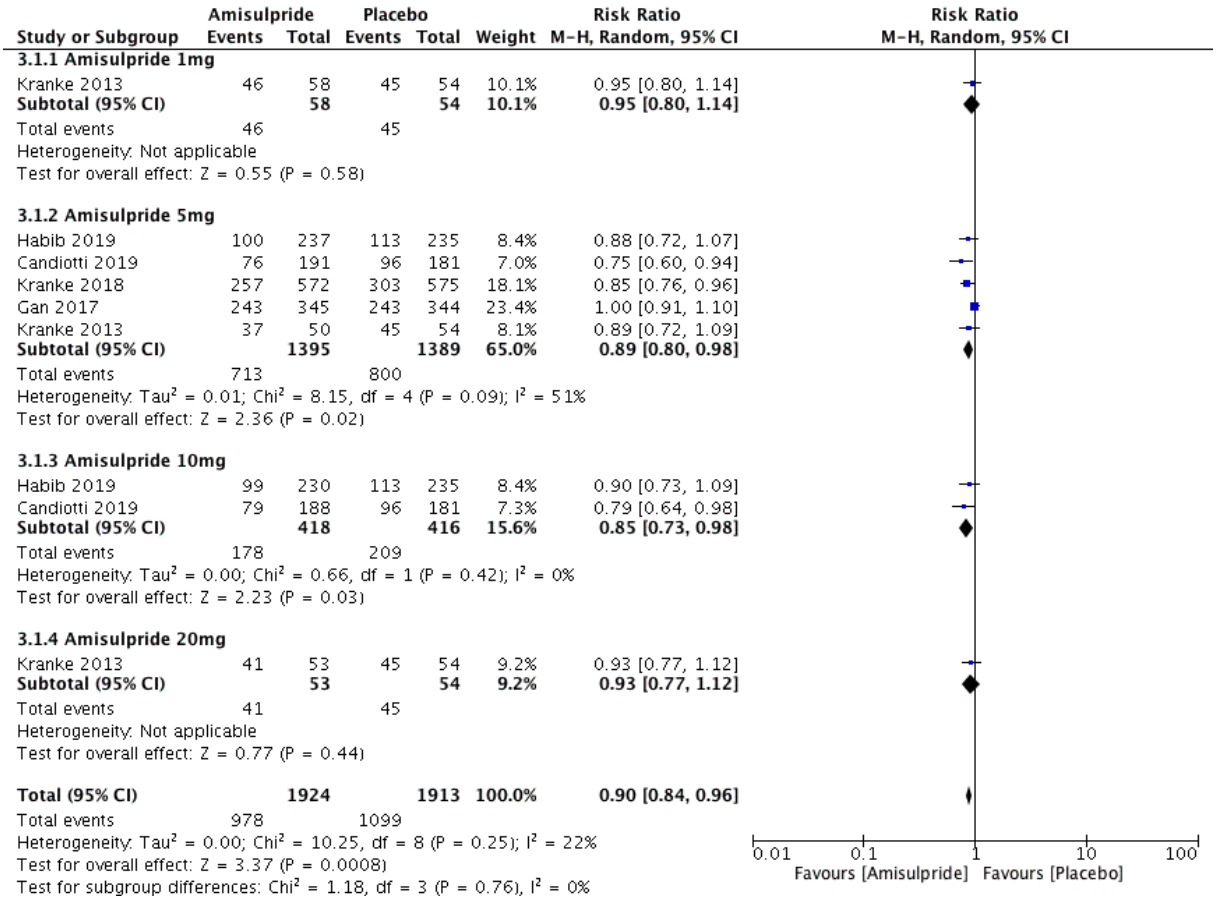

Figure 5. *Forest plot showing the incidence of treatment emergent adverse events occurring 24 hours after surgery or study drug administration.*

3.4.3 Severe Adverse Events (SAE)

The meta-analysis showed no significant difference in the incidence of SAE between amisulpride and placebo group (RR= 0.95; 95% CI, 0.65–1.39, p=0.79) (Figure 6).

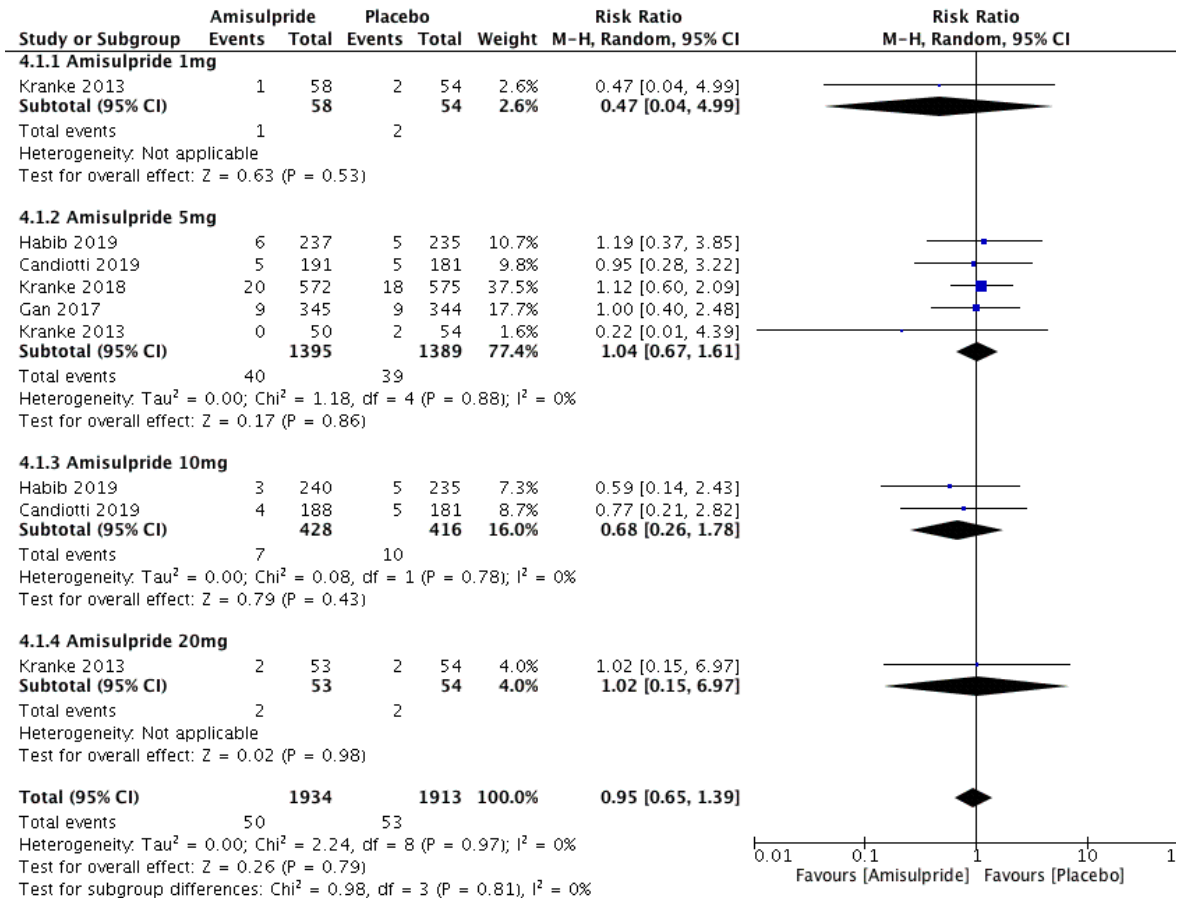

Figure 6. *Forest plot showing the incidence of severe adverse events occurring 24 hours after surgery or study drug administration.*

3.4.4 Life-threatening Adverse Events

There was no significant difference in the incidence of life-threatening adverse events between amisulpride and placebo groups (RR= 0.41; 95% CI, 0.13–1.28, p=0.13) (Figure 7).

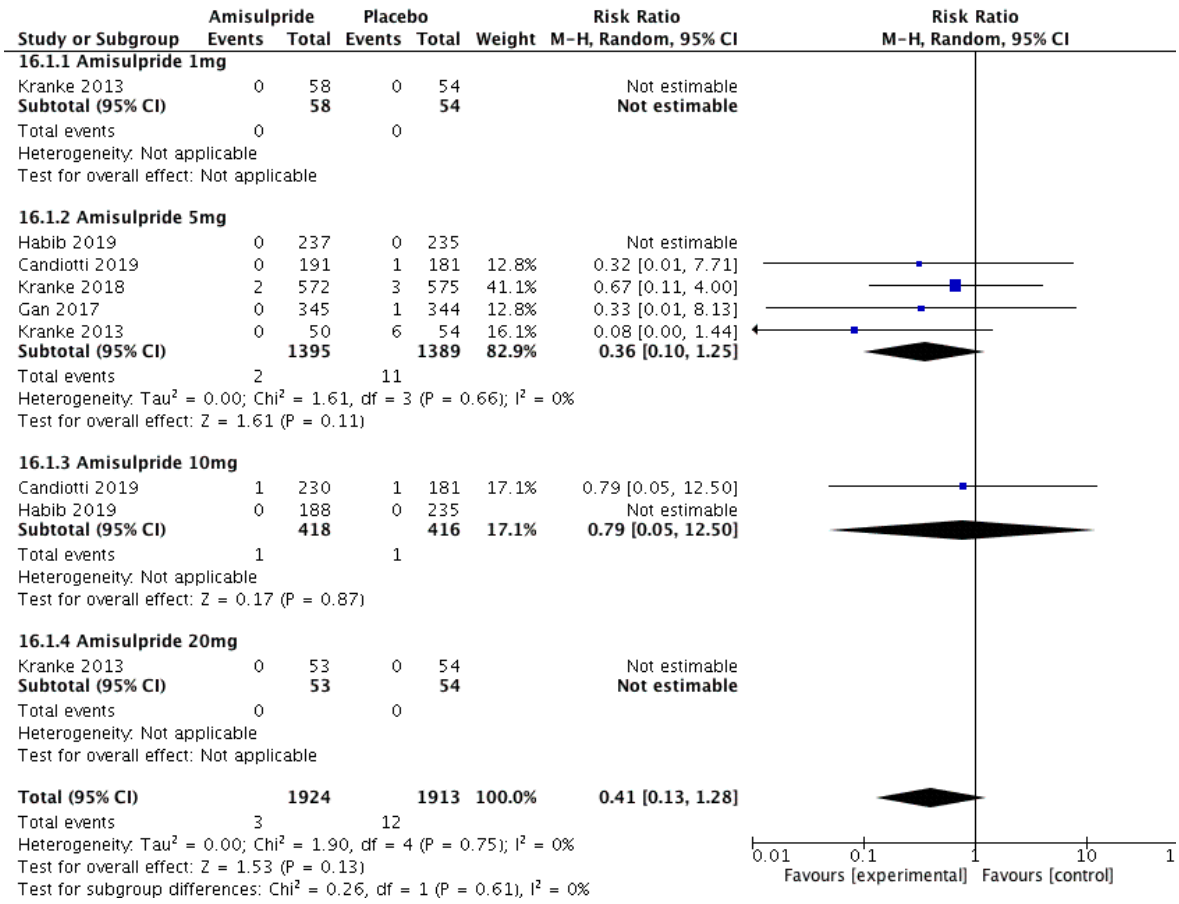

Figure 7. *Forest plot showing the incidence of life-threatening adverse events occurring 24 hours after surgery or study drug administration.*

3.4.5 Insomnia

The incidence of insomnia/sleep disorder, reported in one study (Kranke et al. 2013) was found to be significantly higher in the amisulpride group than in the placebo (RR= 2.13; 95% CI, 0.99–4.57, p=0.05) (Figure 8).

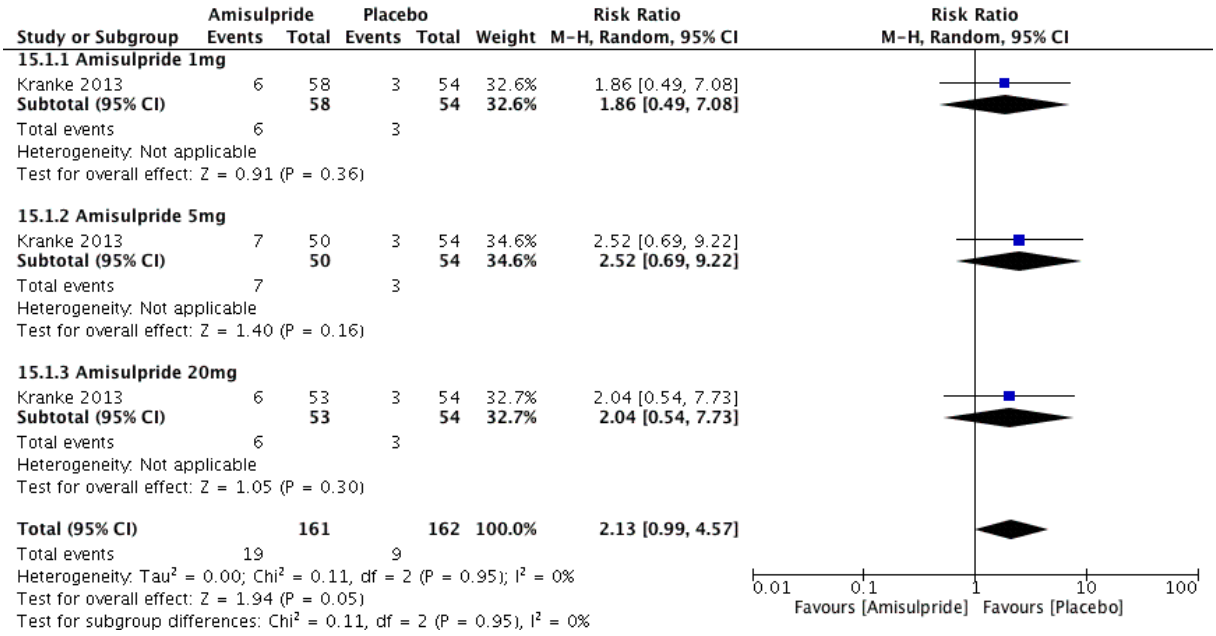

Figure 8. *Forest plot showing the incidence of insomnia occurring 24 hours after surgery.*

3.4.6 Blood prolactin increased

There was a larger increase in blood prolactin levels, as observed in the Gan et al. study, in the amisulpride group as compared to placebo (RR= 8.97; 95% CI, 2.75–29.30, p=0.0003) (Figure 9).

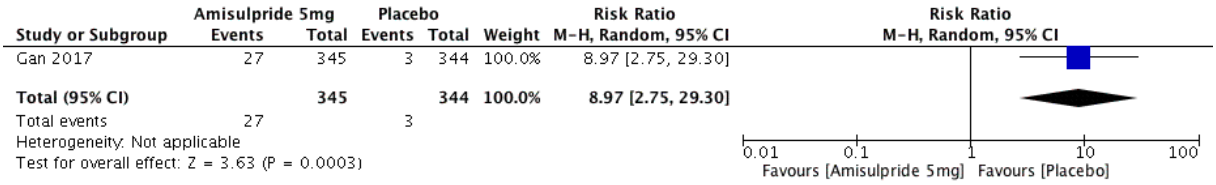

Figure 9. *Forest plot showing the incidence of hyperprolactinaemia occurring 24 hours after study drug administration.*

3.4.7 Pyrexia

Pyrexia was reported in just one study with no significant difference between the amisulpride and placebo groups (RR= 4.72; 95% CI, 0.55–40.87, p=0.16) (Figure 10).

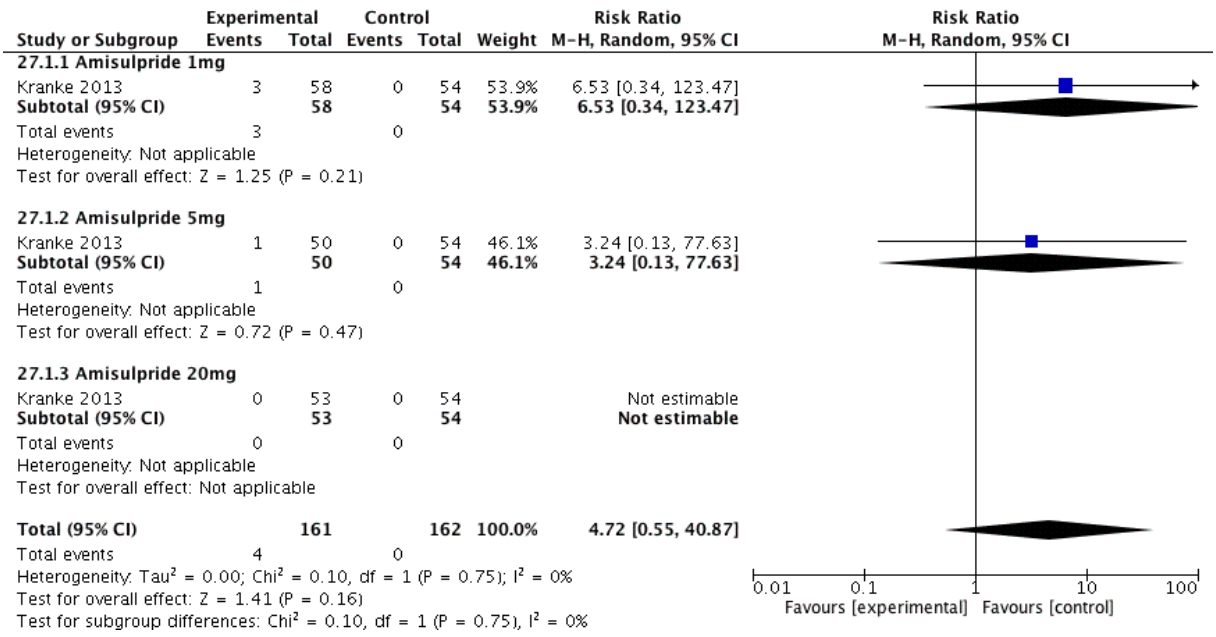

Figure 10. *Forest plot showing the incidence of pyrexia occurring 24 hours after study drug administration.*

3.4.8 Abdominal distension

Abdominal distension was an endpoint in one study with no significant difference between the study groups (RR= 1.63; 95% CI, 0.78–3.40, p=0.19) (Figure 11).

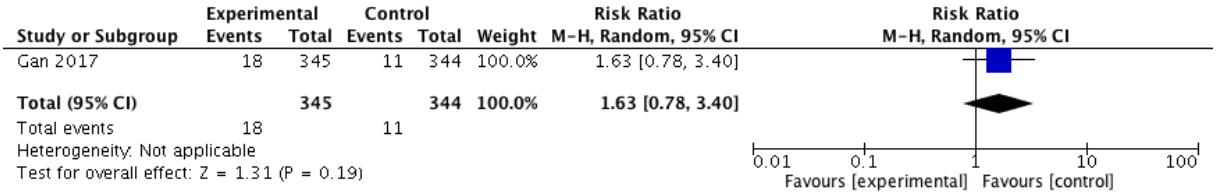

Figure 11. *Forest plot showing the incidence of abdominal distension occurring 24 hours after study drug administration.*

3.4.9 Nausea and Vomiting

"The meta-analysis showed no significant difference in the incidence of nausea (RR = 0.93; 95% CI, 0.77–1.13, p = 0.47) and vomiting (RR = 0.860; 95% CI, 0.52-1.24, p = 0.32), excluding events occurring in the first 24 hours after the end of surgery or the study drug administration, reported as a TEAE in four and two studies, respectively." (Smyla et al.2019) (Figure 12, Figure 13).

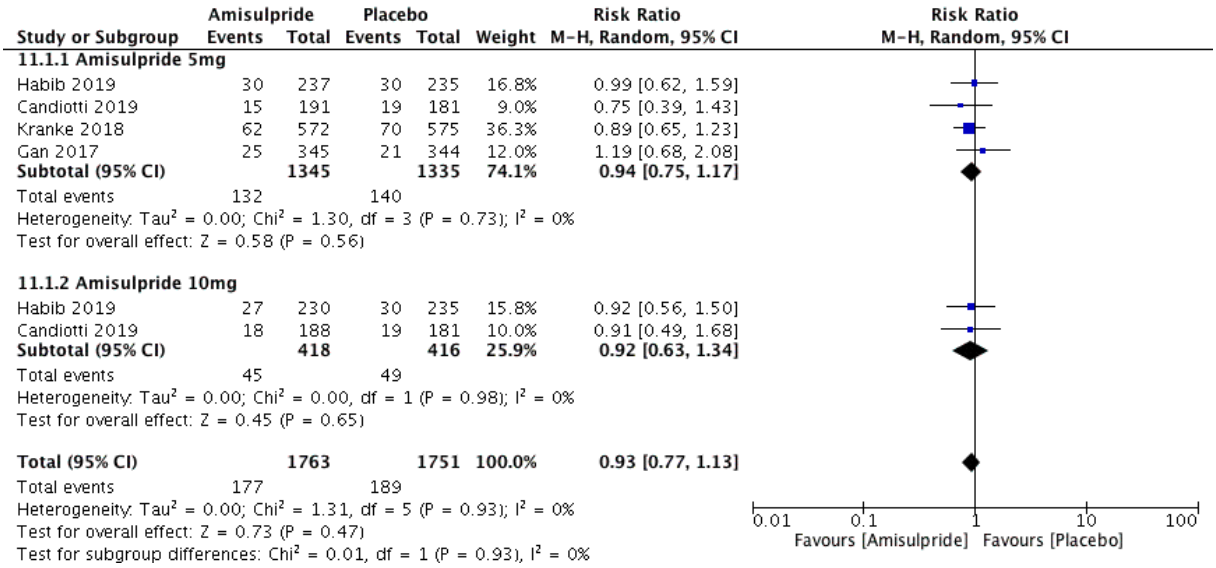

Figure 12. *Forest plot showing the incidence of nausea excluding events occurring 24 hours after surgery or study drug administration.*

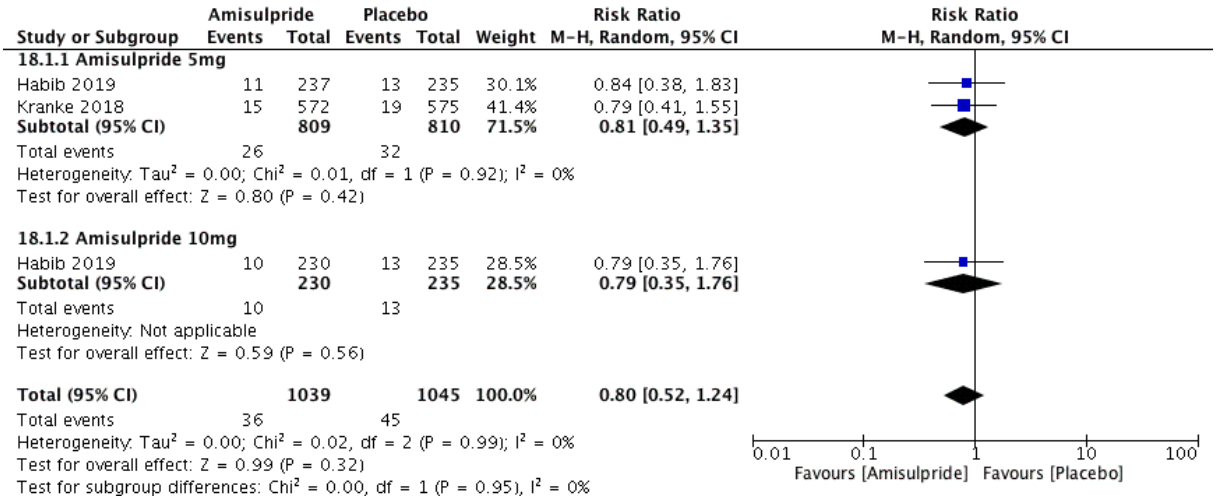

Figure 13. *Forest plot showing the incidence of vomiting excluding events occuring 24 hours after surgery or study drug administration.*

3.4.10 Hypertension

Hypertension was detected as an adverse event in one study with no significant differences between the study arms (RR= 1.99; 95% CI, 0.49–8.06, p=0.33) (Figure 14).

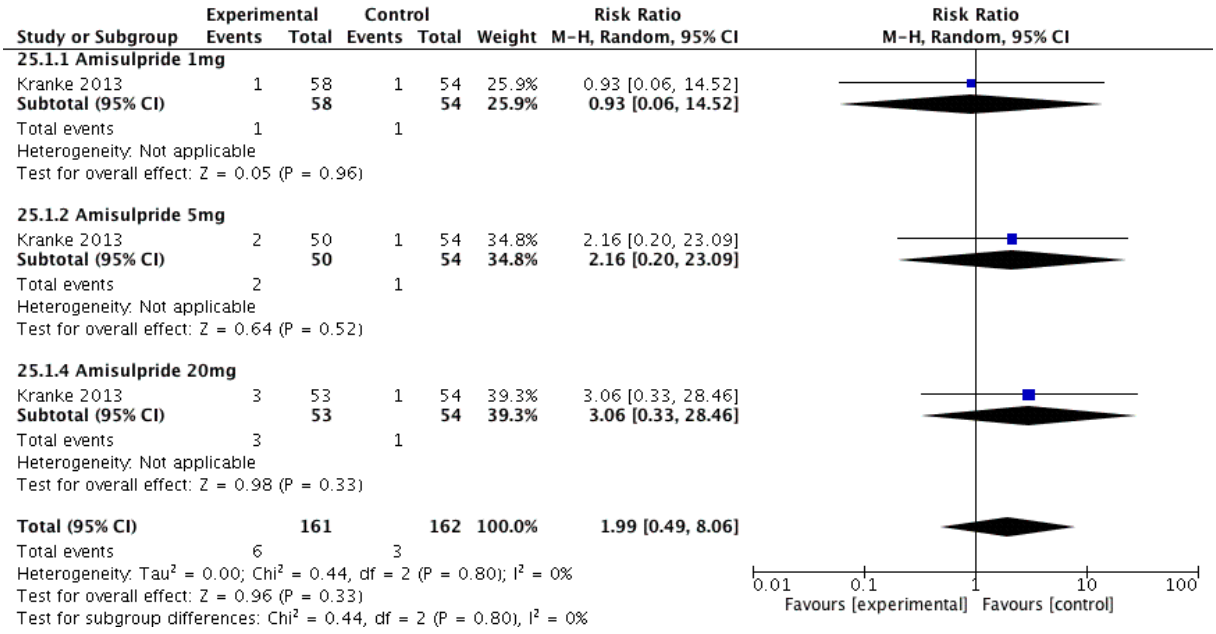

Figure 14. *Forest plot showing the incidence of hypertension occurring 24 hours after study drug administration.*

3.4.11 Flatulence

Four studies observed flatulence as an adverse effect. No significant difference was found between the amisulpride and placebo groups (RR= 0.89; 95% CI, 0.69–1.14, p=0.83) (Figure 15).

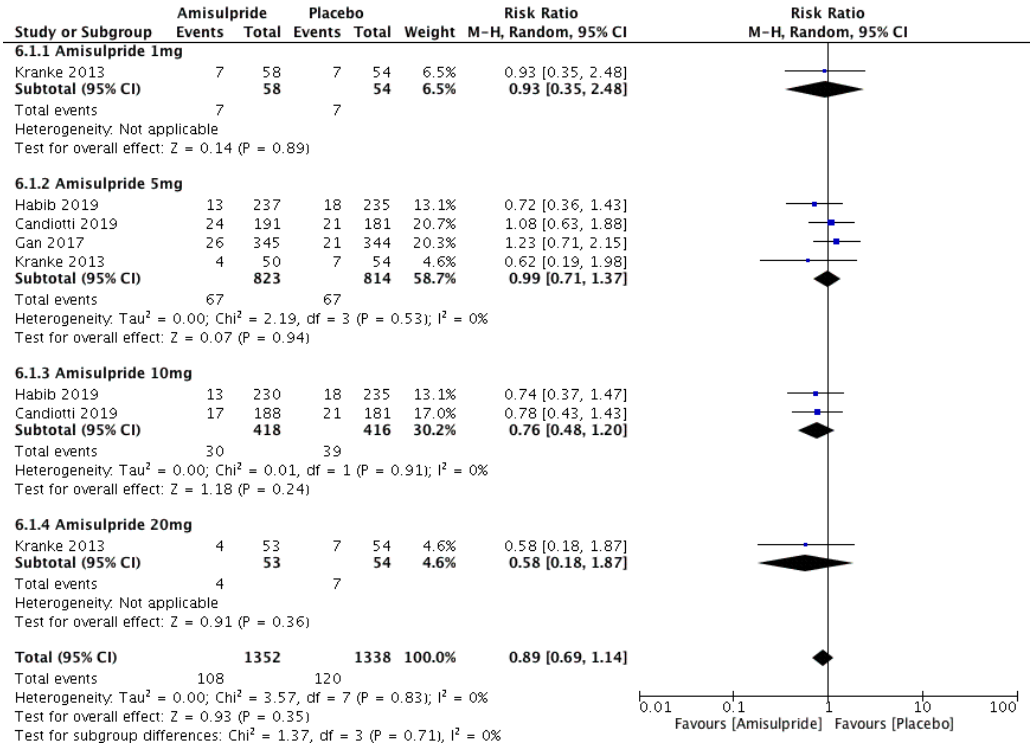

Figure 15. *Forest plot showing the incidence of flatulence 24 hours after surgery or study drug administration.*

3.4.12 Constipation

All 5 studies evaluated the rate of constipation. The pooled analysis showed no significant difference between amisulpride and placebo group (RR= 0.91; 95% CI, 0.71–1.20, p=0.43) (Figure 16).

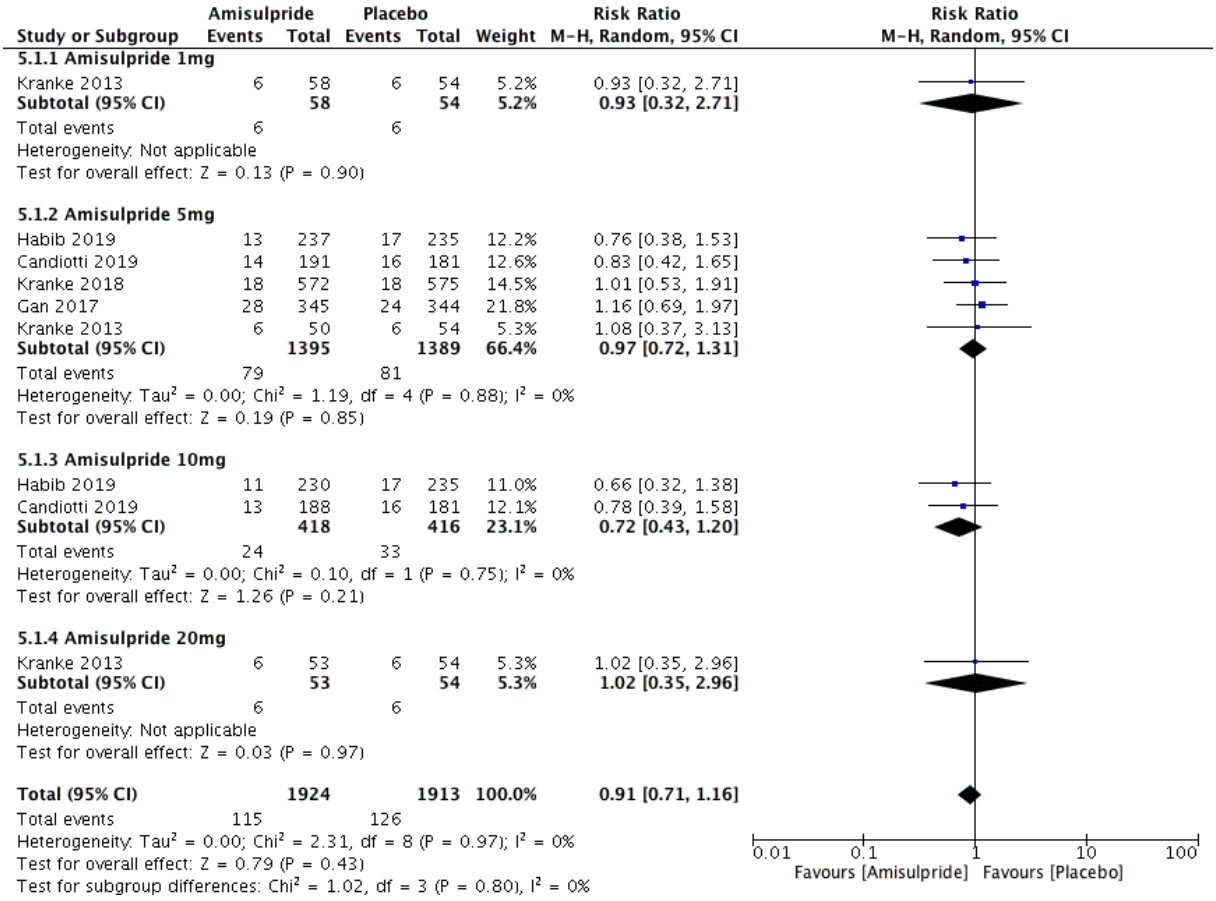

Figure 16. *Forest plot showing the incidence of constipation 24 hours after surgery or study drug administration.*

3.4.13 Chills

The meta-analysis showed no significant difference in the incidence of chills, as reported in one study (RR= 1.26; 95% CI, 0.66–2.40, p=0.49) (Figure 17).

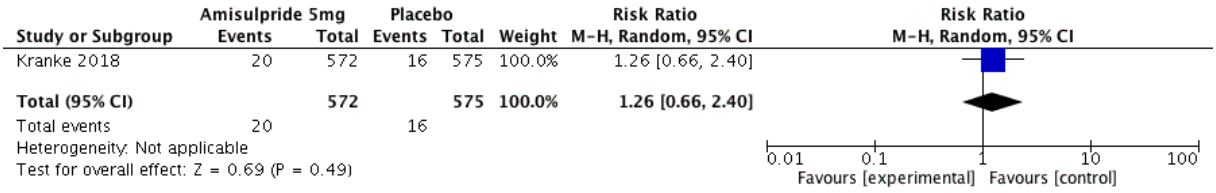

Figure 17. *Forest plot showing the incidence of constipation 24 hours after surgery.*

3.4.14 Pruritus

A total of two studies reported pruritus as an adverse event. The meta-analysis showed no significant difference between amisulpride and placebo group (RR= 0.86; 95% CI, 0.55–1.35, p=0.89) (Figure 18).

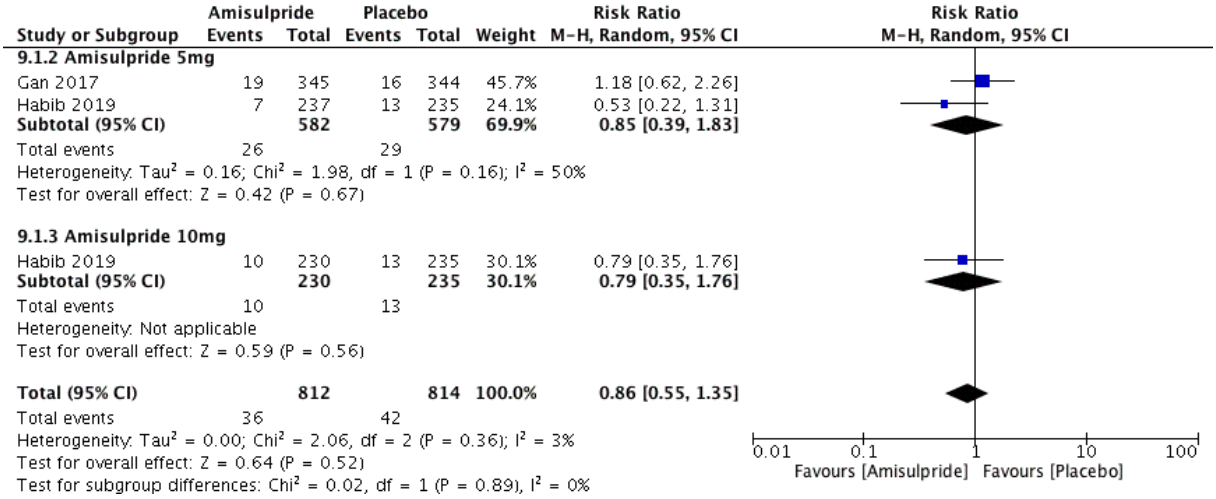

Figure 18. *Forest plot showing the incidence of pruritus 24 hours after surgery or study drug administration.*

3.4.15 Anaemia

Two studies reported anaemia as a TEAE. The pooled analysis revealed no significant difference between amisulpride and placebo group (RR= 1.19; 95% CI, 0.70–2.04, p=0.52) (Figure 19).

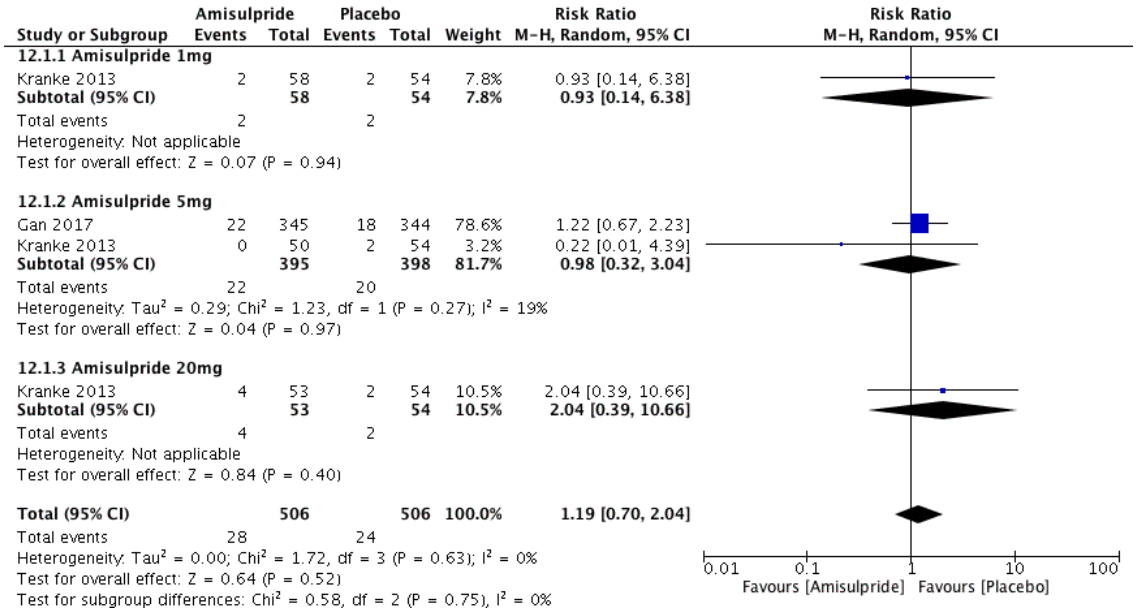

Figure 19. *Forest plot showing the incidence of anaemia 24 hours after surgery.*

3.4.16 Hyperglycemia

The occurrence of hyperglycemia, as reported in one study, did not differ between amisulpride and placebo group (RR= 0.87; 95% CI, 0.56–1.35, p=0.52) (Figure 20).

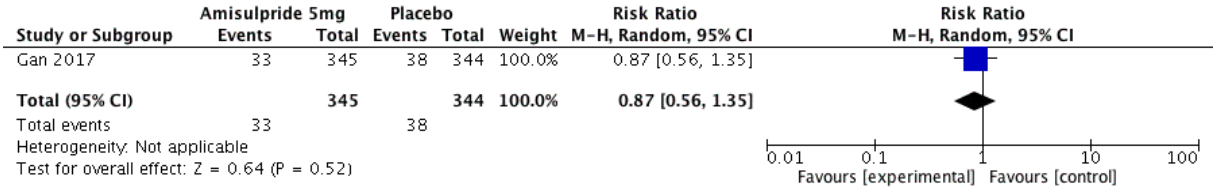

Figure 20. *Forest plot showing the incidence of hyperglycemia 24 hours after surgery.*

3.4.17 Leukocytosis

Only the Gan et al. study reported leukocytosis as an adverse event, which did not differ significantly between amisulpride and placebo group (RR= 1.13; 95% CI, 0.66–1.94, p=0.66) (Figure 21).

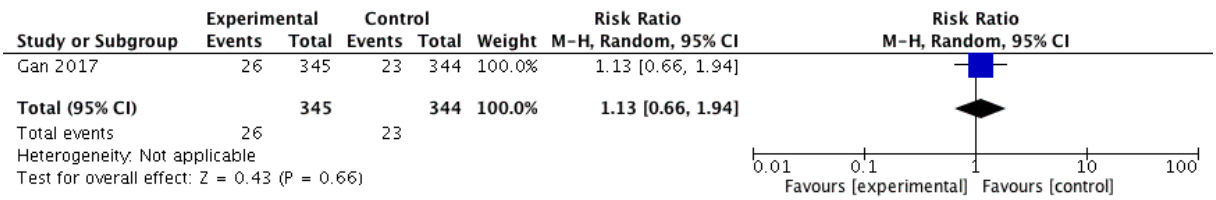

Figure 21. *Forest plot showing the incidence of leukocytosis 24 hours after surgery.*

3.4.18 Dizziness

The meta-analysis showed no difference between the amisulpride and placebo groups in the incidence of dizziness, as reported in one study. (RR= 0.76; 95% CI, 0.21–2.73, p=0.48) (Figure 22).

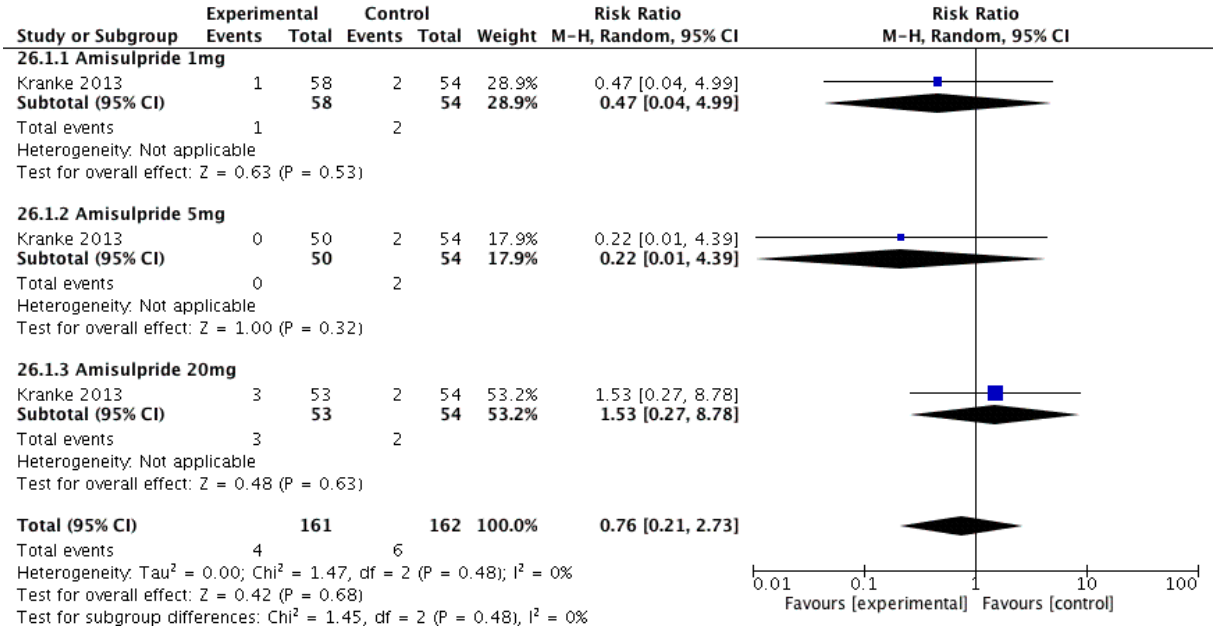

Figure 22. *Forest plot showing the incidence of dizziness 24 hours after surgery.*

3.4.19 Hypotension

Three of the included trials reported hypotension as an adverse event, with no difference in the incidence between amisulpride and placebo group. (RR= 1.05; 95% CI, 0.69–1.59, p=0.82) (Figure 23).

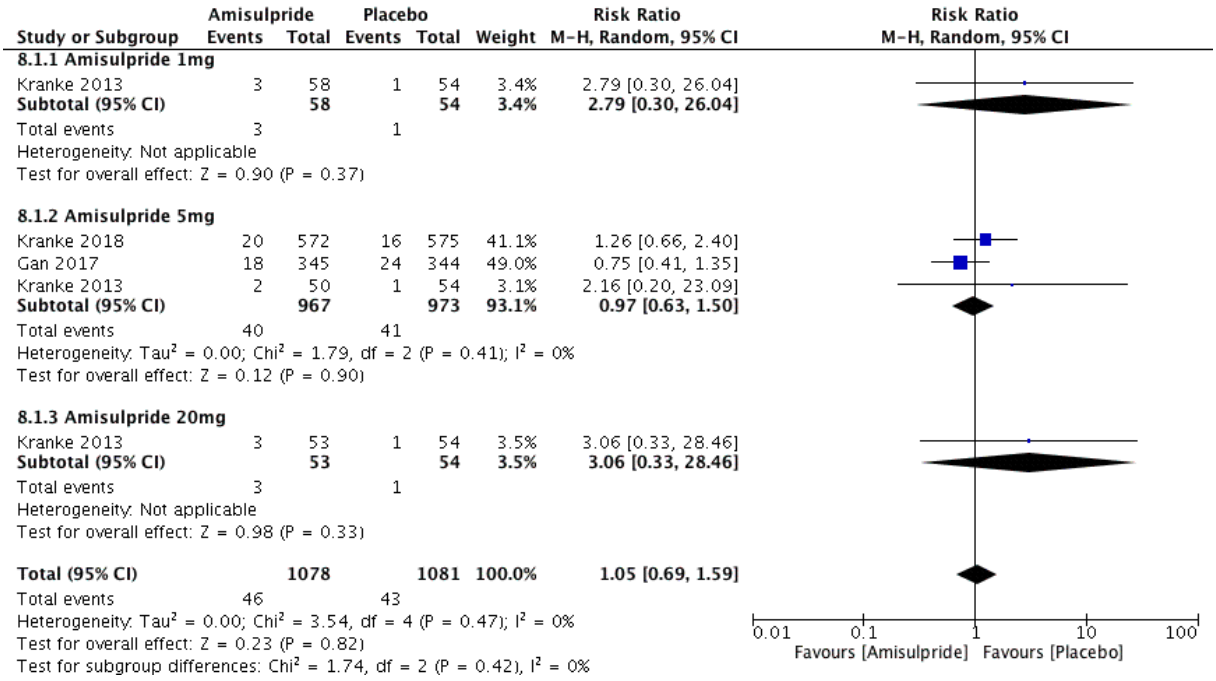

Figure 23. *Forest plot showing the incidence of hypotension 24 hours after surgery.*

3.4.20 Pain

Procedural pain was reported in 3 studies (Kranke et al. 2013, Gan et al. 2017, Kranke et al. 2018), while 2 studies reported infusion site pain (Candiotti et al. 2018; Habib et al. 2019). The pooled analysis of the available data showed no significant difference between amisulpride and placebo group (RR= 1.01; 95% CI, 0.90–1.13, p=0.64) (Figure 24).

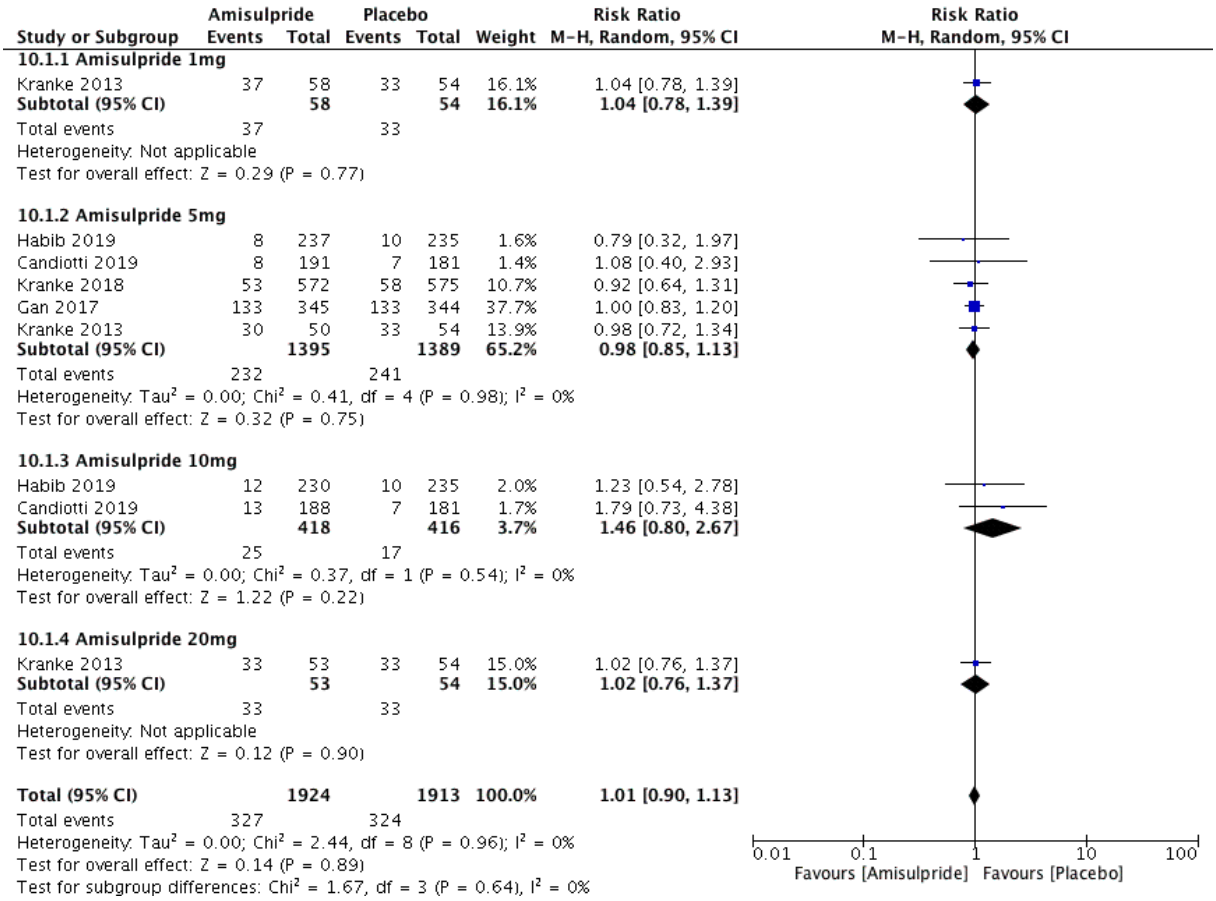

Figure 24. *Forest plot showing the incidence of pain 24 hours after surgery or study drug administration.*

3.4.21 Hypoproteinemia

The incidence of hypoproteinemia, reported in one study, did not vary between the amisulpride and placebo group (RR= 1.04; 95% CI, 0.62–1.74, p=0.90) (Figure 25).

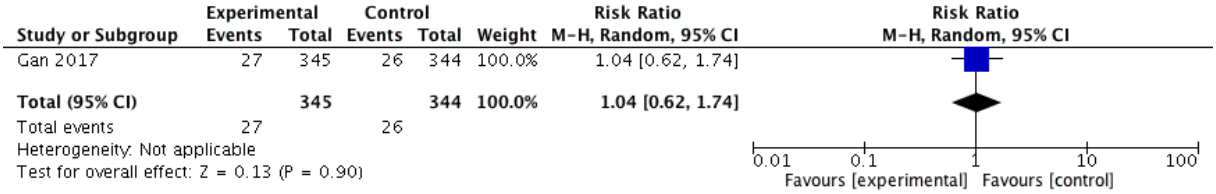

Figure 25. *Forest plot showing the incidence of hypoproteinemia 24 hours after surgery.*

3.4.22 Headache

Four studies evaluated the rate of headache. The pooled analysis showed no significant difference between intervention and placebo group (RR= 1.00; 95% CI, 0.50–1.97, p=0.99) (Figure 26).

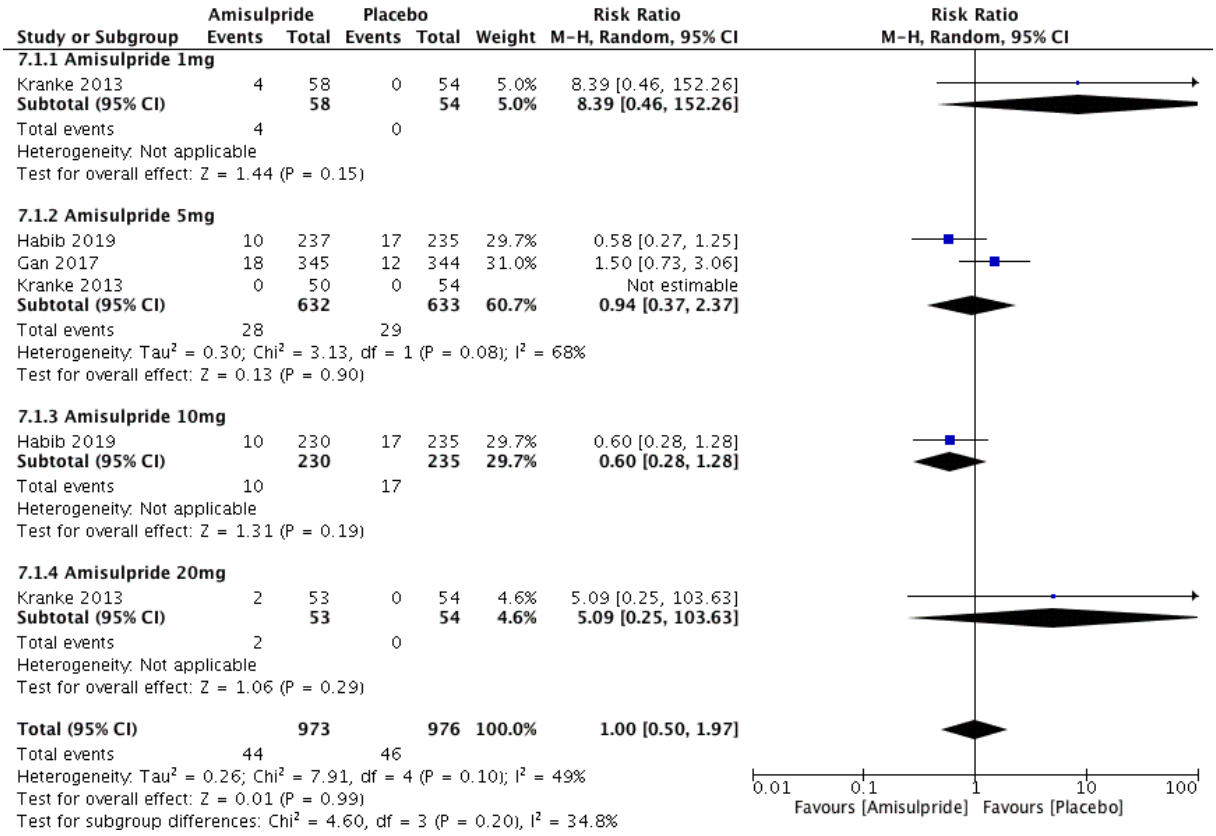

Figure 26. *Forest plot showing the incidence of headache 24 hours after surgery or study drug administration.*

3.4.23 Hypocalcaemia

Hypocalcaemia was reported as a TEAE in one study. Its incidence was not statistically significant between amisulpride and placebo group (RR= 1.00; 95% CI, 0.61–1.62, p=0.99) (Figure 27).

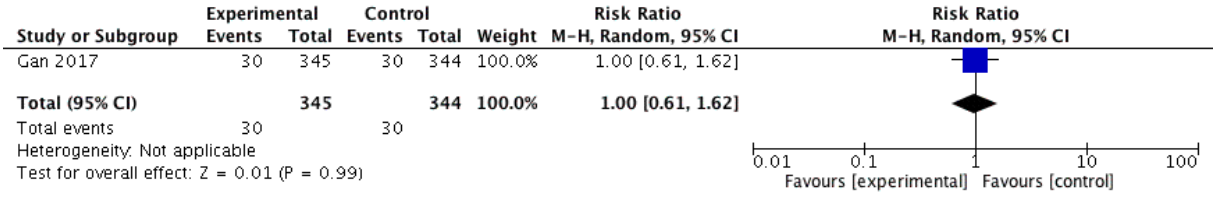

Figure 27. *Forest plot showing the incidence ofhypocalcamie 24 hours after surgery.*

3.4.24 Summary of safety outcomes for intravenous amisulpride

Table 3 summarizes the pooled risk ratios with 95% confidence intervals for each safety outcomes between the amisulpride and placebo groups (Smyla et al. 2019).

3.5 *Risk of bias assessment*

The risk of bias in all trials included in the meta-analysis was evaluated as low by two independent investigators. All trials were sponsored by Acacia Pharma Ltd, Cambridge, UK. A contract research organization monitored the trials and the external audits were performed by the FDA.

Table 3. *Meta-analysis of overall adverse events; N, number of patients; TEAE, treatment-emergent adverse event; SAE, severe adverse event; AE, adverse event. (Adapted from Smyla et al. 2019).*

Outcome	Studies	N	RR (95% CI)	p-value	
Blood prolactin increased	1	689	8.97 [2.75, 29.30]	0.0003	p value ≤ 0.05
any TEAE	5	3313	0.90 [0.84, 0.96]	0.0008	
Insomnia	1	215	2.13 [0.99, 4.57]	0.05	
any life-threatening AE	5	3313	0.41 [0.13, 1.28]	0.13	p value > 0.05
Pyrexia	1	215	4.72 [0.55, 40.87]	0.16	
Abdominal distension	1	689	1.63 [0.78, 3.40]	0.19	
Vomiting*	2	1849	0.80 [0.52, 1.24]	0.32	
Hypertension	1	215	1.99 [0.49, 8.06]	0.33	
Flatulence	4	2166	0.89 [0.69, 1.14]	0.35	
Constipation	5	3313	0.91 [0.71, 1.16]	0.43	
Nausea*	4	3098	0.93 [0.77, 1.13]	0.47	
Chills	1	1147	1.26 [0.66, 2.40]	0.49	
Pruritus	2	1391	0.86 [0.55, 1.35]	0.52	
Anaemia	2	904	1.19 [0.7, 2.04]	0.52	
Hyperglycemia	1	689	0.87 [0.56, 1.35]	0.52	
Leukocytosis	1	689	1.13 [0.66, 1.94]	0.66	
Dizziness	1	215	0.76 [0.21, 2.73]	0.68	
any SAE	5	3313	0.95 [0.65, 1.39]	0.79	
Hypotension	3	2051	1.05 [0.69, 1.59]	0.82	
Pain	5	3313	1.01 [0.90, 1.13]	0.89	
Hypoproteinemia	1	689	1.04 [0.62, 1.74]	0.9	
Headache	3	1606	1.00 [0.50, 1.97]	0.99	
Hypocalcemia	1	689	1.00 [0.61, 1.62]	0.99	

***Excluding nausea and vomiting within 24 hours after the end of surgery or study drug administration**

4. Discussion

This meta-analysis shows that prophylactic use of intravenous amisulpride effectively reduces the risk of PONV and rescue medication use in the 24-hour postoperative period as well as up to 24 hours after its therapeutic use with an overall lower incidence of adverse events as compared to the placebo group.

The only adverse events which occurred more frequently in patients receiving amisulpride were insomnia and elevated serum prolactin levels, however, their clinical relevance is questionable. Insomnia, which was reported in the study of Kranke et al., first occurred more than 48 h after amisulpride administration, which is significantly more than 5-fold the half-life of the intravenous dose (Kranke et al. 2013).

Hyperprolactinaemia is a common side effect of dopamine receptor antagonists, caused by the D_2 antagonism on the anterior pituitary lactotroph cells with subsequent loss of the inhibition of prolactin secretion (Kim et al. 2012). The mean prolactin increase in the Gan et al. study was small and did not exceed the norm for non-pregnant women (Gan et al. 2017). The effect of a single 10 mg IV amisulpride dose on prolactin levels appears to be short-lived, with a 10-fold increase at 1 hour, with prolactin levels returning to the norm by 12 hours (Fox et al. 2019).

Common side effects associated with the use of dopamine antagonists include extrapyramidal symptoms, such as tremor, akathisia, bradykinesia, Parkinson-like rigidity, acute dystonia and tardive dyskinesia, yet none of such symptoms were reported in the studies on the IV amisulpride for PONV, which is consistent with a recent meta-analysis involving data from psychiatric population studies (Huhn et al. 2019).

The main concern associated with the use of dopamine antagonists is its cardiovascular toxicity. Amisulpride was shown to be cardiovascular-safe in the psychiatric population, where doses up to 1200 mg per day are administered daily (Coulouvrat and Dondey-Nouvel 1999). However, an overdose (4-80 g) can lead to QTc prolongation and the development of severe cardiac arrhythmias, such as torsade de pointes (Isbister et al. 2010). Low doses of 5 mg IV tested for PONV do not lead to the QTc interval prolongation, while higher, supratherapeutic doses (40 mg IV) prolong the QTc interval by 23.4 ms from baseline, never exceeding absolute QTcF value of > 500 ms. Therefore, the QTc interval prolongation seems to be dose-dependent (Täubel et al. 2017).

Current therapy guidelines for PONV recommend multimodal prevention approach, including a combination therapy regimen with various classes of antiemetics to achieve optimal

results (Gan et al. 2020). Due to safety concerns raised by the FDA in 2001, when the black-box warning was issued on droperidol, which was once a first-line therapy agent for PONV, its use has significantly declined, leading to the search for alternative antiemetics targeting the dopamine receptor (Habib and Gan 2008). The most obvious candidate, haloperidol, frequently used for the treatment of psychosis and agitation, was also labeled with a black-box warning in 2007 due to the risk of QTc prolongation (Gan et al. 2014). Another potential candidate, metoclopramide, was proven to be effective only at higher doses, which are associated with higher incidence of adverse events including extrapyramidal symptoms, hypotension and tachycardia. Therefore, it is also not recommended as a first-line therapy (Wallenborn et al. 2006). Another representative of phenothiazine group, perphenazine was proven effective at 5 mg doses for preventing PONV, however data on the timing, route of application and the most effective dose is very limited (Schnabel et al. 2010). Amisulpride, with its favourable safety profile and low risk of drug interactions emerges as the most interesting potential substitute to droperidol, particularly in patients with a high cardiovascular risk profile.

Even though the black-box warning for droperidol remains controversial, with studies proving that low doses (< 1 mg or < 15 μg/kg) are effective and cardiocascular-safe, many clinicians stopped using droperidol after 2001. This was not only for safety reasons, but also due to its lack of its availability after voluntary withdrawal from the market by the manufacturer, which in turn led to decrease in its use, mostly in the United States. However, in the majority of European countries, droperidol was still administered as an antiemetic or its withdrawal was only temporary like in the United Kingdom or in Spain (Schaub et al. 2012).

A possible limitation of the trials included in the meta-analysis is that most of the participants were female patients (87,5%), therefore the results might not represent the whole surgical population; nonetheless, women are much more prone to suffer from PONV than men (Smyla et al. 2019).

Another limitation is that all recruited patients were adults, thus the efficacy and safety of intravenous amisulpride in children remains unknown. However, dopamine antagonists are not recommended as a first line PONV therapy due to the generally increased susceptibility of paediatric population to this pharmacological class (Smyla et al.2019).

The amount of studies available so far on intravenous amisulpride for PONV prophylaxis and treatment is very limited. The pooled effect estimates with 95% confidence interval were statistically significant, but reach the areas of clinical irrelevance (RR 0.8-1.25); therefore more clinical trials with more participants and broader inclusion criteria are needed to overcome this

limitation. Furthermore, studies comparing amisulpride to well-known antiemetics such as dexamethasone or ondansetron are necessary to evaluate its clinical relevance.

In February 2020 Barhemsys, the repurposed intravenous formula of amisulpride hasd gained its FDA approval for both prevention and therapy of PONV. The recently published Fourth Consensus Guidelines for The Management of Postoperative Nausea and Vomiting recommend a 5 mg dose at induction of anaesthesia as a part of a multimodal antiemetic approach (Gan et al. 2020). Amisulpride's success on the market will mostly depend on its cost-effectiveness. Nowadays, the costs of generic formulations of droperidol are low, while the brand-new intravenous formula of amisulpride will lack such cost efficiency (Smyla et al.2020).

In conclusion, intravenous amisulpride emerges as an effective and safe antiemetic for both prevention and treatment of postoperative nausea and vomiting. It can be used in mono- and combination therapy with other antiemetics as a part of a multimodal management of PONV. It's favourable safety profile, no relevant QTc interval prolongation, low risk of drug interactions make it the most interesting representative of the dopamine antagonist group of antiemetics. Further studies on intravenous amisulpride with active controls are needed to compare its efficacy to well-established antiemetics such as dexamethasone and ondansetron.

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6. Summary

Background: Despite the advances in anesthesiology, postoperative nausea and vomiting (PONV) with its complex aetiology still remains a common postoperative complication for many patients. Dopamine D_2-antagonist droperidol was a frequently used cost-effective antiemetic up until 2001, when the FDA issued a black-box warning in its label. Since then, more focus has been put on the research on alternative agents blocking the dopamine receptor.

In 2010, a repurposed formula of intravenous amisulpride, an atypical antipsychotic, which has been on the market for over thirty years, was patented and since then various clinical trials were started to study its antiemetic potential in the management of PONV.

Objectives: The purpose of this meta-analysis was to evaluate the efficacy and safety of intravenous amisulpride on both prevention and treatment of PONV from the clinical data available so far.

Methods: A systematic review (meta-analysis) was conducted according to the 2009 PRISMA guidelines. Two independent investigators searched MEDLINE (PubMed), ClinicalTrials.gov and Cochrane Controlled Register of Trials (CENTRAL) databases for randomized, controlled trials on intravenous amisulpride without language or publication year restrictions. Studies with intervention group receiving intravenous amisulpride for prophylaxis or treatment of PONV as compared to placebo or another antiemetic were included in the meta-analysis. The primary endpoint of the study was the incidence of PONV (any episode of retching/vomiting or use of rescue medication) 24-hours postoperatively or 24-hours after IV amisulpride administration. Rescue medication use 24 hours after operation or study drug administration and the incidence of the most frequent treatment-emergent adverse events (TEAEs) were secondary endpoints of the study. Results were calculated using the Mantel-Haenszel Method and presented as relative risk (RR) with 95% confidence interval (CI).

Results: Data of five eligible trials (n=3313) were included in the final meta-analysis. Three of those trials investigated amisulpride for the prophylaxis of postoperative nausea and vomiting; while two studies analysed amisulpride versus placebo as treatment of PONV. The pooled effect estimate of all trials revealed a significant decrease in the incidence of PONV (RR = 0.78; 95% CI, 0.72–0.85, $p < 0.00001$) in patients receiving amisulpride as compared to placebo. Subgroup analysis according to the administered dose showed that only 1 and 5 mg and not 20 mg amisulpride doses significantly reduced the risk of PONV. Both 5 mg (RR = 0.9; 95% CI, 0.83–0.98; $p = 0.02$) and 10 mg amisulpride doses (RR = 0.85; 95% CI, 0.77–0.93; p

= 0.0004) significantly reduced the incidence of PONV up to 24 hours after treatment with overall RR of 0.87 (95% CI; 0.82–0.93, p < 0.0001). Safety results showed a significant decrease in adverse events (AEs) in the amisulpride group as compared to placebo (RR = 0.9; 95% CI, 0.84-0.96; *P* = 0.008). Out of all the reported AEs, only increased blood prolactin level (RR = 8.97; 95% CI, 2.75-29.30; *P* = 0.0003) and insomnia (RR = 2.13; 95% CI, 0.99-4.57; *P* = 0.05), both reported in 1 study, occurred significantly more frequently in the amisulpride than the placebo group.

Conclusions: This meta-analysis shows that prophylactic use of intravenous amisulpride effectively reduces the risk of PONV and rescue medication use in the 24-hour postoperative period as well as up to 24 hours after its therapeutic use with overall lower incidence of adverse events as compared to placebo. It can be used in mono- and combination therapy with other antiemetics as a part of multimodal management of PONV. It's favourable safety profile, no relevant QTc interval prolongation, low risk of drug interactions make it the most interesting potential droperidol substitute. Further studies on intravenous amisulpride with active controls are needed to compare its efficacy to well-established antiemetics such as dexamethasone and ondansetron.

7. Zusammenfassung

Hintergrund: Trotz der Fortschritte in der Anästhesiologie, bleibt postoperative Übelkeit und Erbrechen (PONV) mit ihrer komplexen Ätiologie bleibt für viele Patienten immer noch eine häufige postoperative Komplikation. Dopamin-D2-Antagonist Droperidol war bis 2001 ein häufig verwendetes und kostengünstiges Antiemetikum, bis die FDA eine Black-Box-Warnung herausgab. Seitdem wurde mehr Wert auf die Erforschung alternativer Wirkstoffe gelegt, die den Dopaminrezeptor blockieren.

Im Jahr 2010 wurde eine neue, intravenöse Formel von Amisulprid, einen atypischen Antipsychotikum, das seit über 30 Jahren auf dem Markt verfügbar ist, patentiert.

Seitdem wurden diverse klinische Studien gestartet, um dessen antiemetisches Potenzial bei der Behandlung von PONV zu untersuchen.

Ziele der Studie: Ziel dieser Metaanalyse war es, die Wirksamkeit und Verträglichkeit von intravenösem Amisulprid sowohl bei der Prävention als auch bei der Behandlung von PONV anhand der bisher verfügbaren klinischen Daten zu bewerten.

Methoden: Die Metaanalyse wurde gemäß den PRISMA-Richtlinien von 2009 durchgeführt.

Zwei unabhängige Prüfer durchsuchten die Datenbanken MEDLINE (PubMed), ClinicalTrials.gov und Cochrane Controlled Register of Trials (CENTRAL) nach randomisierten, kontrollierten Studien zu intravenösem Amisulprid ohne Einschränkungen hinsichtlich der Sprache oder dem Erscheinungsjahr. Studien mit Interventionsgruppen, die intravenöses Amisulprid zur Prophylaxe oder Behandlung von PONV im Vergleich zu Placebo oder einem anderen Antiemetikum erhielten, wurden in die Metaanalyse einbezogen. Der primäre Endpunkt der Studie war die Inzidenz von PONV (jede Episode von Würgen / Erbrechen oder die Gabe von antiemetischer Rescue-Medikation) 24 Stunden postoperativ oder 24 Stunden nach intravenöser Verabreichung von Amisulprid. Antiemetische Rescue-Behandlung 24 Stunden nach der Operation oder der Verabreichung des Studienmedikaments sowie die Inzidenz der häufigsten behandlungsbedingten unerwünschten Ereignissen waren sekundäre Endpunkte der Studie. Die Ergebnisse wurden unter Verwendung der Mantel-Haenszel-Methode berechnet und als relatives Risiko (RR) mit einem Konfidenzintervall von 95% (CI) dargestellt.

Ergebnisse: Daten von fünf geeigneten Studien (n = 3313) wurden in die endgültige Metaanalyse einbezogen. Drei dieser Studien untersuchten Amisulprid zur Prophylaxe von

PONV; in den zwei anderen Studien wurde Amisulprid im Vergleich zu Placebo als Behandlung von PONV getestet. Die gepoolte Effektschätzung aller Studien ergab eine signifikante Abnahme der PONV-Inzidenz (RR = 0,78; 95% CI, 0,72–0,85, p <0,00001) bei Patienten, die Amisulprid erhielten, im Vergleich zu Placebo. Eine Untergruppenanalyse gemäß der verabreichten Dosis zeigte, dass nur 1 und 5 mg, nicht aber 20 mg Amisulprid-Dosen das PONV-Risiko signifikant verringerten. Sowohl 5 mg (RR = 0,9; 95% CI, 0,83–0,98; p = 0,02) als auch 10 mg Amisulprid-Dosen (RR = 0,85; 95% CI, 0,77–0,93; p = 0,0004) reduzierten die Inzidenz von PONV signifikant bis zu 24 Stunden nach der Behandlung mit einem Gesamt-RR von 0,87 (95% CI; 0,82–0,93, p <0,0001). Die Sicherheitsergebnisse zeigten eine signifikante Abnahme von unerwünschten Ereignissen in der Amisulpridgruppe im Vergleich zu Placebo (RR = 0,9; 95% CI, 0,84–0,96; P = 0,008). Von allen berichteten Nebenwirkungen traten in der Amisulpridegruppe im Vergleich zu Placebo nur ein erhöhter Prolaktinspiegel im Blut (RR = 8,97; 95% CI 2,75-29,30; P = 0,0003) und erhöhte Schlaflosigkeit (RR = 2,13; 95% CI 0,99-4,57; P = 0,05) signifikant häufiger auf. Beiden wurden in einer Studie berichtet.

Schlussfolgerungen: Diese Metaanalyse zeigt, dass die prophylaktische Anwendung von intravenösem Amisulprid das Risiko von PONV- und antiemetischer Rescue-Medikation in der 24-Stunden-Postoperationsperiode sowie bis zu 24 Stunden nach der therapeutischen Anwendung wirksam verringert, wobei die Häufigkeit unerwünschter Ereignisse im Vergleich zu Placebo insgesamt geringer ist. Amisulpride kann in der Mono- und Kombinationstherapie mit anderen Antiemetika als Teil des multimodalen Managements von PONV eingesetzt werden. Das vorteilhafte Verträglichkeitsprofil, keine relevante Verlängerung des QTc-Intervalls und das geringe Risiko von Arzneimittelwechselwirkungen machen es zum interessantesten potenziellen Droperidolersatz. Weitere Studien zu intravenösem Amisulprid mit aktiven Kontrollen sind erforderlich, um seine Wirksamkeit mit etablierten Antiemetika wie Dexamethason und Ondansetron zu vergleichen.

8. Appendix

8.1 *Reprints of publications*

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Clarivate Analytics

Review Article

Amisulpride for the prevention and treatment of postoperative nausea and vomiting: A quantitative systematic review (meta-analysis)

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Contents

Summary

Background: Postoperative nausea and vomiting (PONV) is a distressing complication of surgery. Droperidol has been widely used as an antiemetic for several decades. As a result of the Food and Drug Administration's "black box" warning on droperidol, research on alternative drugs acting on dopamine receptors has been intensified. Amisulpride is an atypical antipsychotic drug first introduced in France in 1986 and since then approved for the treatment of acute and chronic schizophrenia in many countries. Recently, a new formula of an aqueous solution of amisulpride suitable for intravenous injection was developed. Objectives: The aim of this review is to highlight the basic pharmacological profile and to report a meta-analysis on the safety and efficacy of intravenous amisulpride for the prevention and treatment of PONV. Methods: According to the 2009 PRISMA guidelines, a systematic search of MEDLINE via PubMed, ClinicalTrials.gov and Cochrane Controlled Register of Trials (CENTRAL) for randomized, controlled trials, without restrictions, was conducted by two independent investigators (Dec 2013-Feb 2019). Randomized, controlled trials, reporting the incidence of PONV in patients undergoing general anesthesia with an intervention group, receiving amisulpride either as prophylaxis or treatment compared to placebo or active interventions, were included in the meta-analysis. The primary endpoint was the incidence of PONV, defined as any episode of vomiting/retching or any use of antiemetic rescue medication 24 hours after operation or study drug administration. Secondary endpoints included the incidence of rescue antiemetic use within the 24-hour postoperative period or 24 hours after amisulpride administration, as well as the incidence of adverse events. Meta-analysis was performed using a random-effects model and data are presented as RR (relative risk) with 95% confidence interval (CI). Results: Data of 5 placebo-controlled studies including 3,313 patients were finally included in the meta-analysis. Three studies investigated the prevention of PONV while 2 studies compared amisulpride to placebo in the treatment of PONV. Intravenously administered amisulpride during surgery decreased the risk of PONV compared to placebo (RR = 0.78; 95% CI, 0.72-0.85; P<0.00001). Subgroup analysis according to dose of the intervention suggested no relevant dose effect. However, the number of included studies was small. Treatment of PONV with 5 and 10 mg amisulpride decreased the risk of PONV in the following 24 hours compared to placebo (RR 0.87; 95% CI, 0.82-0.93; P<0.0001). There was no difference between 5 and 10 mg amisulpride detectable. There was a significantly lower risk of postoperative adverse events with amisulpride as compared to placebo (RR=0.9; 95% CI, 0.84-0.96; P=0.008). There was no significant difference in the risk of severe adverse events (RR=0.95, 95% CI, 0.65-1.39; P=0.79). Conclusions: The meta-analysis demonstrates that intravenous amisulpride effectively reduced the risk of PONV in patients undergoing general anesthesia within the first 24 hours postoperatively as well as within 24 hours after therapeutic use when administered as an antiemetic rescue medication. However, there are currently few studies investigating amisulpride as prophylaxis and treatment for PONV. The estimated effects reached statistical significance, but included areas

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of clinical nonrelevance (RR > 0.8). Furthermore, a comparison of amisulpride with the recommended dose of 5 mg against well-known active interventions for prevention of PONV, such as ondansetron or dexamethasone, are necessary to put the presented results into context. Future trials may also investigate other patient populations, e.g., pediatric patients.

Key words: Amisulpride – Postoperative nausea and vomiting – Dopamine D_2/D_3 receptor antagonist – Meta-analysis

Background

Postoperative nausea and vomiting (PONV) is a frequent complication associated with general anesthesia. Nowadays, with modern anesthetics and new classes of antiemetic drugs, PONV still occurs in approximately 20-30% of all patients undergoing surgery and in up to 80% of the patients with a high-risk profile (1, 2). Although often referred to as a big "little" problem (3), PONV may lead to dehydration and electrolyte imbalances, wound dehiscence and other severe complications, such as aspiration of the gastric contents, esophageal rupture, pneumothorax, subcutaneous emphysema as well as loss of vision (4, 5). PONV is a leading cause of dissatisfaction with anesthesia. Not surprisingly, patients are willing to pay up to USD 100 for a completely effective therapy (6-8). Furthermore, it can be an economical issue due to a prolonged stay in the recovery room after surgery, additional antiemetic medication, extra nursing time, delays in discharge, and, finally, unplanned readmission in the outpatient setting (8-11).

Droperidol, a relatively selective D_2 receptor antagonist, has been widely used as an antiemetic for several decades (12, 13). Doses ranging from 0.625 to 1.25 mg i.v. have been shown to be effective for PONV prophylaxis (2). However, in 2001, the U.S. Food and Drug Administration (FDA) issued a "black box" warning based on cases of QTc prolongation and serious cardiac arrhythmias, such as torsades de pointes (TdP) (14, 15). The "black box" is used to highlight serious and life-threatening adverse events (AEs) and inform about precautions as well as implement restrictions so that the serious adverse reactions can be prevented (16). The FDA recommended that all patients should receive a 12-channel electrocardiogram before droperidol administration in order to assess if a prolonged QT interval (QTc interval of ≥ 460 ms in women and ≥ 450 ms in men) is present, and in these cases droperidol use is considered contraindicated. Furthermore, a continuous electrocardiogram monitoring up to 2-3 hours after treatment should be performed in patients that received droperidol (17, 18). Since droperidol is usually administered at the end of surgery, additional monitoring creates additional workload. As a result of these concerns, research on alternative drugs acting on dopamine receptors has recently been intensified (2, 14, 15).

Amisulpride is an atypical antipsychotic drug first introduced in France in 1986 under the name Solian and since then approved for the treatment of positive and negative symptoms of acute and chronic schizophrenia in many European countries as well as in Australia (19, 20). The recommended doses of oral amisulpride for patients with negative symptoms are 50-300 mg/day, 400-800 mg/day for patients with psychotic episodes, but in individual cases the dose can be increased up to 1200 mg/day (20).

Amisulpride is rapidly absorbed after oral administration and has a biphasic absorption profile. The first plasma peak concentration occurs after 1 h (C_{max} = 42.3 ± 3.3 ng/mL) followed by a second one between 3 and 4 h (C_{max} = 55.7 ± 3.7 ng/mL). The absolute bioavailability of a 50-mg amisulpride tablet is about 50%. Amisulpride is rapidly and widely distributed to the body tissues with a volume of distribution of 5.8 L/kg (21, 22). The lack of inhibition of the cytochrome P450 and low plasma protein binding (17%) contribute to low propensity for drug interactions (21). Metabolism of amisulpride is minimal and the two main metabolites are inactive. Amisulpride is primarily excreted in an unchanged form in urine (22-25% after oral and almost 50% after intravenous administration) and in feces. The terminal plasma elimination half-life ($t_{½}$) is approximately 7-8 h after intravenous and 12 h after oral dose. Renal clearance ranges from 17 to 20 L/h (330 mL/min) (23, 24). Amisulpride has a safe pharmacokinetic profile in elderly patients, in which no dose modification seems to be necessary (22). However, in patients with renal failure the doses might have to be adjusted, as amisulpride's peak plasma concentration increases linearly with the degree of renal impairment (25).

Amisulpride shows high affinity and selectivity for dopamine D_2 (K_i = 2.8 nM) and D_3 (K_i = 3.2 nM) receptors, mainly those localized in the limbic system rather than in the striatum. At low doses, amisulpride blocks presynaptic dopamine receptors, resulting in an increased dopamine transmission, while at higher doses it blocks postsynaptic D_2/D_3 receptors (26, 27). It has low affinity to adrenergic, muscarinic, histamine, serotonin (with the exception of 5-HT_{2B} and 5-HT_{7A}) as well as dopamine D_1, D_4 and D_5 receptors (23, 28).

Amisulpride tablets are practically insoluble in water (20). Since intravenous application is the preferred route for antiemetic administration in the perioperative setting, recently a new, patent-protected formula of aqueous citrate-buffered solution of amisulpride, suitable for intravenous injection, was developed for the treatment of nausea and vomiting (29).

This meta-analysis of amisulpride trials was conducted to evaluate the safety and efficacy associated with its use for prevention and treatment of PONV and provide clinicians with a summary of the efficacy data available for amisulpride so far.

Material and Methods

Search strategy and study selection

This meta-analysis was carried out and reported according to the 2009 PRISMA guidelines (30). A systematic literature search of MEDLINE (via PubMed), Cochrane Controlled Register of Trials (CENTRAL) and ClinicalTrials.gov for randomized, controlled trials, without language or publication year restrictions, was conducted by two independent investigators.

The following search terms were used: ("sultopride" OR "sultopride" OR "amisulpride") AND ("postoperative nausea and vomiting" OR ("postoperative" AND "nausea" AND "vomiting" OR "postoperative nausea and vomiting" OR "ponv").

Randomized, controlled trials, reporting the incidence of PONV in patients undergoing general anesthesia with an intervention group, receiving amisulpride either as prophylaxis or treatment compared to placebo or active interventions, were included in the meta-analysis. Criteria for exclusion were nonrandomized trials, review articles and animal studies.

Data extraction

Study selection, data extraction process as well as risk of bias assessment were performed by two independent authors (NS and LE). Mendeley Version 1.19.2 was used for reference management and duplicate removal. Data extraction was performed using a modified Cochrane data collection form (31). Risk of bias assessment was determined by means of the Cochrane Collaboration's tool. In case of a disagreement, a consensus was reached with a third investigator.

The primary endpoint was the incidence of PONV, defined as any episode of vomiting/retching or any use of antiemetic rescue medication 24 hours after operation or study drug administration.

Secondary endpoints included the incidence of rescue antiemetic use within the 24-hour postoperative period or 24 hours after amisulpride administration as well as the incidence of any treatment-emergent AEs (TEAEs), any severe AEs and the most frequent TEAE associated with intravenous amisulpride administration, such as constipation, flatulence, headache, hypotension, anemia, procedural pain, nausea, vomiting and pruritus.

Statistical analysis and risk of bias assessment

Random-effects meta-analysis was employed to integrate the data from the studies and calculate the pooled effect estimate of intravenous amisulpride on PONV and pooled risk estimates for AEs. Effects and AEs were expressed as RR (relative risk) with 95% confidence interval (CI) and calculated using the Mantel–Haenszel Method. The heterogeneity of the results was measured using the χ-square and I^2 statistic. *P* values < 0.05 were considered statistically significant. A subgroup analysis was performed for different doses of amisulpride. To illustrate the results, Forest plots were created. Cochrane risk-of-bias tool for randomized trials was used to assess the potential risk of bias in all included studies (32). The meta-analysis was carried out using ReviewManager (RevMan) [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Study selection

A total of 9 publications were identified, 2 of which were removed due to duplication. Two studies were excluded based on their title and available abstract. Data of 5 eligible, full-text randomized, placebo-controlled studies with 3,313 patients were extracted and included in the final meta-analysis (Fig. 1).

Included studies' characteristics

The 5 analyzed articles (33-37) were published between December 2013 and February 2019. One study consisted of 2 identical trials conducted in Europe and the United States; thus, the pooled results were used for the meta-analysis (34).

A total of 3 studies investigated amisulpride for the prevention of PONV; 2 of those studies used amisulpride as mono-prophylaxis, while 1 of the studies combined one additional antiemetic with amisulpride or placebo (see Table I). Another 2 studies compared amisulpride to placebo in the treatment of PONV (the study of Candiotti et al. in patients with no prior prophylaxis, and the study of Habib et al. in patients that received up to three standard antiemetics).

The details of each study, including number of patients, percentage of women participating in the study, baseline PONV risk, type of anesthesia as well as prior PONV prophylaxis are listed in Table I.

Efficacy of intravenous amisulpride on the prevention and treatment of PONV

Three studies investigated intravenous amisulpride in 1-, 5- and 20-mg (33) or 5-mg doses (34, 35) as prophylaxis of PONV in the 24-hour period after surgery. PONV was defined as vomiting/retching (emesis) or use of antiemetic rescue. The incidence of nausea was a secondary endpoint in all 3 studies (33-35).

Two studies investigated 5- and 10-mg doses of intravenous amisulpride for treatment of established PONV (vomiting/retching or episode of nausea that occurred up

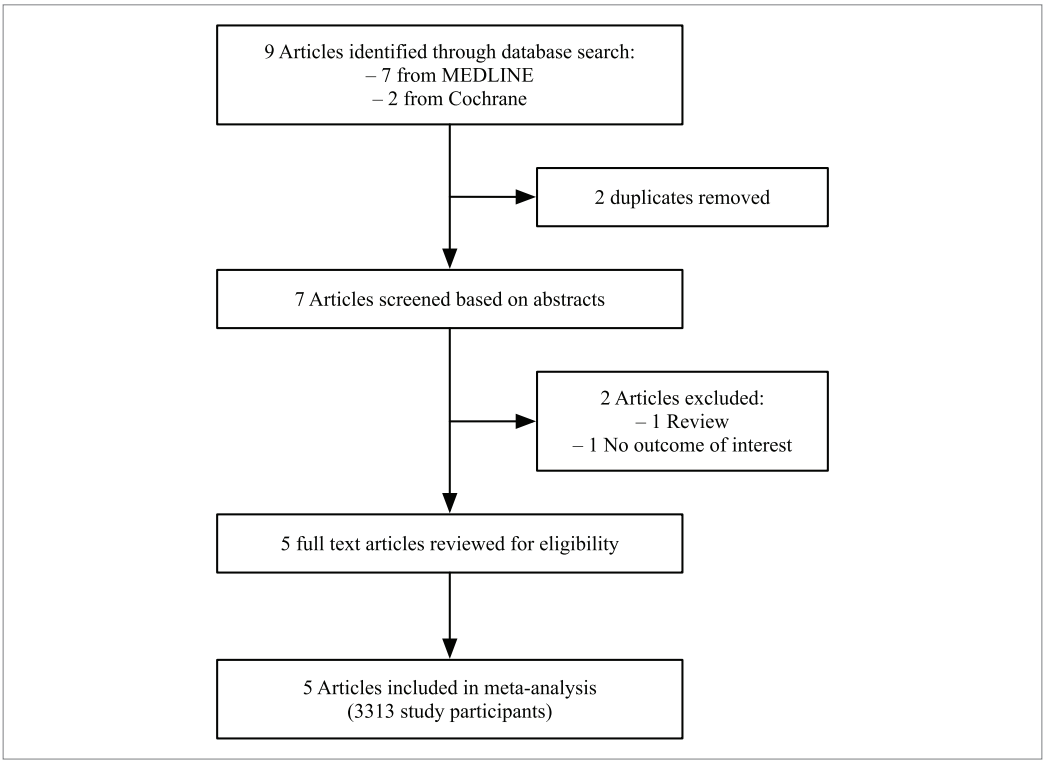

Figure 1. Flowchart of the literature search and study selection process.

to 24 hours after operation and before discharge from the hospital, for which the patients requested an antiemetic). Both studies then assessed the incidence of PONV, defined as emesis or rescue antiemetic use in the 24-hour postoperative period, excluding episodes of emesis in the first 30 minutes (36, 37).

Figure 2 shows the effect of amisulpride 1, 5 and 20 mg on preventing PONV within 24 hours after surgery. The pooled effect estimates of the meta-analysis of all trials showed a significant decreased risk of PONV (RR = 0.78; 95% CI, 0.72-0.85; $P < 0.00001$) with amisulpride compared to placebo. Subgroup analysis according to dose of the intervention suggested no relevant dose effect. However, the number of included studies was small.

Figure 3 shows the efficacy of 5 and 10 mg amisulpride used to treat established PONV. The meta-analysis favored both 5 mg amisulpride (RR = 0.9; 95% CI, 0.83-0.98; $P = 0.02$) and 10-mg doses (RR = 0.85; 95% CI, 0.77-0.93; $P = 0.0004$) with an overall RR of 0.87 (95% CI, 0.82-0.93; $P < 0.0001$). There was no difference between 5 and 10 mg amisulpride detectable.

Use of rescue medication

Figure 4 shows the use of rescue medication in the first 24 hours after surgery or study drug administration. Amisulpride was associated with a significant decrease in rescue medication use as compared to placebo (RR = 0.83; 95% CI, 0.78-0.88, $P < 0.00001$).

Safety of intravenous amisulpride

The pooled risk ratios between amisulpride and placebo with corresponding 95% CIs for each safety outcome are summarized in Table II.

Results of the meta-analysis showed a significantly lower risk of postoperative AEs with amisulpride as compared to placebo (RR = 0.9; 95% CI, 0.84-0.96; $P = 0.008$). There was no significant difference in the risk of severe AEs (RR = 0.95; 95% CI, 0.65-1.39, $P = 0.79$) or potential life-threatening AEs (RR = 0.41; 95% CI, 0.13-1.28; $P = 0.13$) between the two groups. Pain (RR = 1.01; 95% CI, 0.90-1.13; $P = 0.99$) and constipation (RR = 0.89; 95% CI, 0.69-1.14; $P = 0.35$) were reported in all 5 trials, showing no significant difference

Table I. *Characteristics of included studies.*

		Habib 2019 (37)			Candiotti 2019 (36)			Kranke 2018 (35)		Gan 2017 (34)		Kranke 2013 (33)		
		Amisulpride 5 mg	Amisulpride 10 mg	Placebo	Amisulpride 5 mg	Amisulpride 10 mg	Placebo	Amisulpride 5 mg	Placebo	Amisulpride 5 mg	Placebo	Amisulpride 10 mg	Amisulpride 20 mg	Placebo
Number of subjects (n)		237	230	235	191	188	181	572	575	315	311	58	50	53	54
Sex, female %		213 (89.9%)	208 (90.4%)	212 (90.2%)	146 (76.4%)	145 (77.1%)	136 (75.1%)	552 (96.5%)	557 (96.9%)	75%	78%	91%	96%	92%	87%
History of PONV		123 (51.9%)	110 (47.8%)	121 (51.5%)	7 (3.7%)	14 (7.7%)	10 (5.2%)	227 (39.7%)	225 (39.1%)	131 (41.6%)	113 (36.3%)	21 (39%)	21 (36%)	20 (40%)	47 (87%)
Nonsmoker		183 (77.2%)	161 (70%)	166 (70.6%)	7 (3.7%)	2 (1.1%)	119 (62.3%)	516 (90.2)	514 (89.4%)	261 (82.9%)	262 (84.2%)	37 (85%)	42 (84%)	40 (75%)	46 (85%)
Postoperative opioid use		No data			No data			567 (99.1%)	573 (99.7%)	307 (97.5%)	301 (96.8%)	39 (67%)	31 (62%)	37 (70%)	33 (61%)
PONV risk profile		Moderate-to-high risk			Low-to-moderate risk of PONV			3-4 Apfel score risk factors		≥ 2 Apfel score risk factors		≥ 2 Apfel score risk factors			
2 risk factors		17 (7.2%)	10 (4.3%)	7 (3.0%)	66 (35.1%)	66 (36.5%)	70 (36.6%)	1 (0.2%)	1 (0.2%)	88 (27.9%)	89 (28.6%)	24 (41%)	14 (28%)	19 (36%)	16 (30%)
3 risk factors		90 (38%)	108 (47%)	105 (44.7%)	105 (55.9%)	90 (49.7%)	99 (51.8%)	321 (56.1%)	326 (56.7%)	149 (47.3%)	148 (47.6%)	22 (38%)	20 (40%)	22 (42%)	23 (43%)
4 risk factors		129 (54.4%)	111 (48.3%)	121 (51.5%)	7 (3.7%)	9 (5.0%)	12 (6.3%)	250 (43.7%)	248 (43.1%)	78 (24.8%)	74 (23.8%)	12 (21%)	16 (32%)	12 (23%)	15 (28%)
PONV prophylaxis		1-3 standard nondopaminergic antiemetic, most commonly ondansetron, dexamethasone, granisetron or scopolamine			None			One standard nondopaminergic antiemetic, most commonly ondansetron, dexamethasone or betamethasone		None		None			
Type of surgery	Open technique	108 (45.6%)	98 (42.6%)	121 (51.5%)	79 (41.4%)	81 (43.1%)	74 (40.9%)	273 (47.5%)	281 (49.1%)	186 (59%)	194 (62.4%)	69% overall abdominal surgery, 24% breast or axillary surgery; laparoscopic technique was used in 25% of patients			
	Laparoscopic	129 (54.4%)	132 (57.4%)	114 (48.5%)	112 (58.6%)	107 (56.9%)	107 (59.1%)	302 (52.5%)	291 (50.9%)	120 (38.1%)	115 (37%)				
Type of anesthesia		General inhalational anesthesia													

PONV, postoperative nausea and vomiting

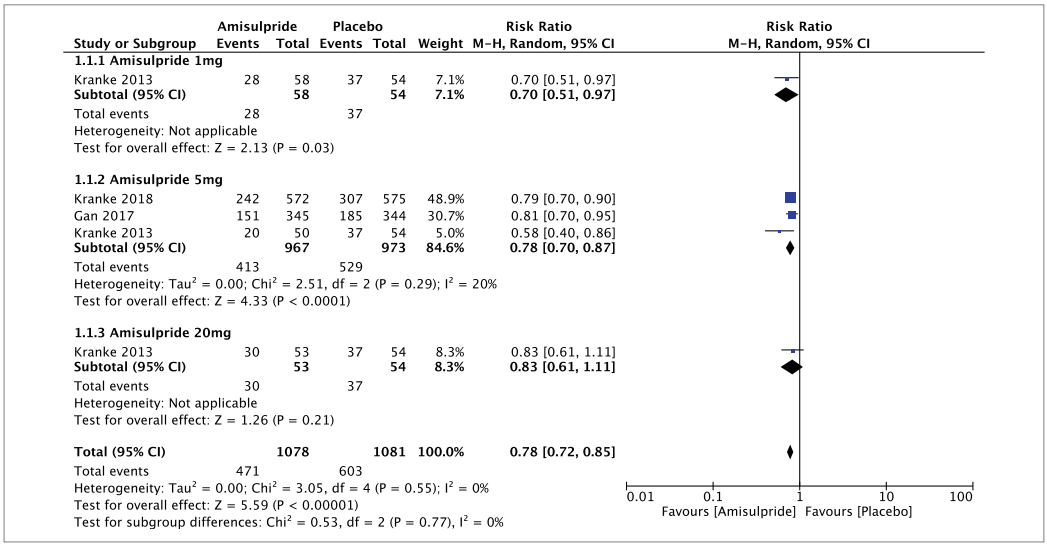

Figure 2. Forest plot of the estimated effect of intravenous amisulpride on prevention of postoperative nausea and vomiting within 24 hours postoperatively.

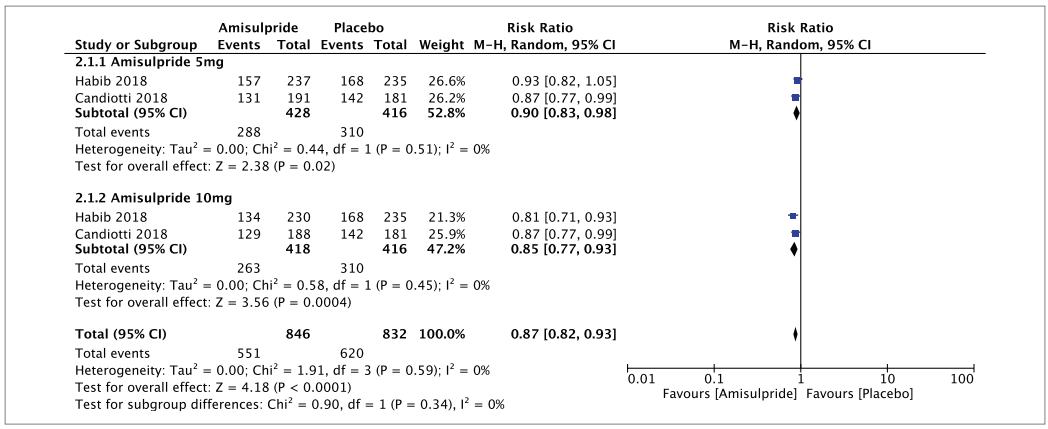

Figure 3. Forest plot of the estimated effect of intravenous amisulpride used to treat established postoperative nausea and vomiting within the following 24 hours.

between amisulpride and placebo. There was also no significant difference in the incidence of flatulence (RR = 0.89; 95% CI, 0.69-1.14; *P* = 0.35), which was reported in 4 studies, headache (RR = 1.00; 95% CI, 0.50-1.97; *P* = 0.99) and hypotension (RR = 1.05; 95% CI, 0.69-1.59; *P* = 0.82), both reported in 3 studies, as well as anemia (RR = 1.19; 95% CI, 0.7-2.04; *P* = 0.52) and pruritus (RR = 0.86; 95% CI, 0.55-1.35; *P* = 0.52), which were reported in 2 trials. The meta-analysis showed no significant difference of amisulpride compared to placebo for nausea (RR = 0.93; 95% CI, 0.77-1.13; *P* = 0.47) and vomiting (RR = 0.860; 95% CI, 0.52-1.24; *P* = 0.32), excluding events occurring in the first 24 hours after the end of surgery or the study drug administration, reported as a TEAE in 4 and 2 studies, respectively. Out of all the AEs which were reported in just 1 study, only the incidence of insomnia/sleep disorder (RR = 2.13; 95% CI, 0.99-4.57; *P* = 0.05) and increase in blood prolactin level (RR = 8.97;

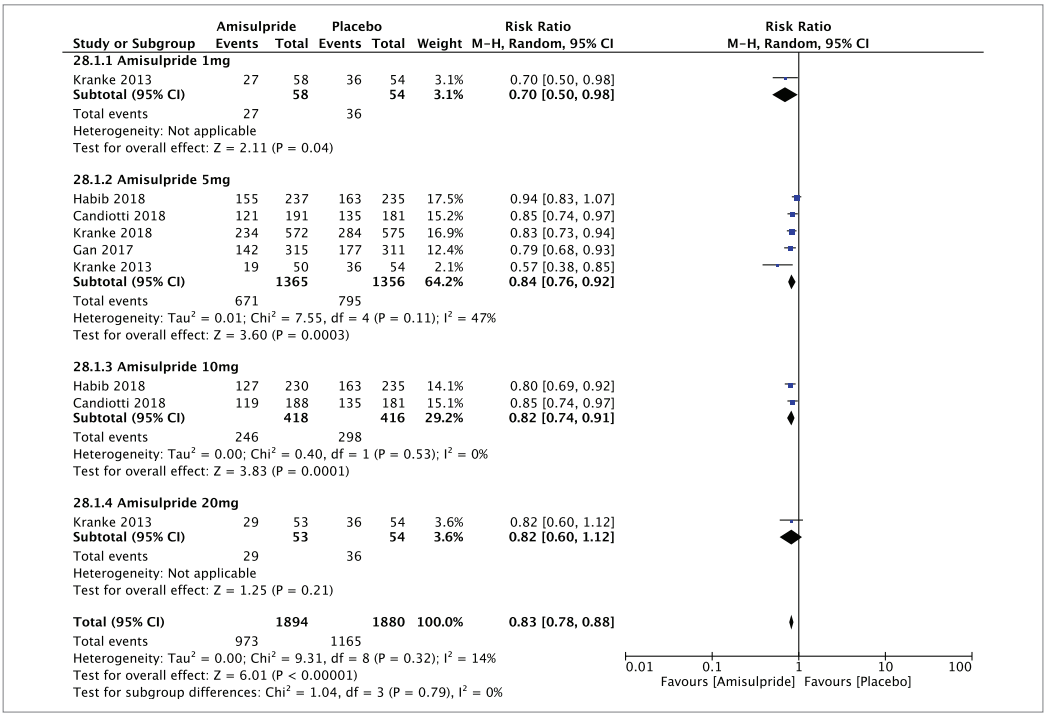

Figure 4. Forest plot for the use of rescue medication 24 hours after surgery or study drug administration.

95% CI, 2.75-29.30; $P = 0.0003$) were found to be significantly higher in the amisulpride group as compared to placebo.

Risk of bias

The overall risk of bias in all 5 trials included in the meta-analysis was classified by 2 independent investigators as low based on the report of the studies. All trials were funded entirely by Acacia Pharma Ltd., Cambridge, UK. An external clinical research organization provided monitoring for the trials and external auditing by the FDA took place.

Discussion

The meta-analysis demonstrates that intravenous amisulpride effectively reduces the incidence of PONV and use of rescue medication in patients undergoing general anesthesia within the first 24 hours postoperatively as well as within 24 hours after therapeutic use when administered as an antiemetic rescue medication.

Amisulpride proved to be a safe antiemetic with lower overall incidence of AEs than placebo, suggesting that efficient PONV management leads to an overall improvement in patients' well-being after surgery (35-37). The only AEs that were observed more frequently in the amisulpride group were elevation in serum prolactin levels as well as insomnia. Hyperprolactinemia can be explained by amisulpride's D_2 antagonism on the lactotroph cells in the anterior pituitary, leading to a loss of dopamine inhibitory effect on prolactin secretion (38). However, the mean prolactin increase after a single-dose amisulpride administration did not exceed the normal levels in nonpregnant women and did not lead to any clinical consequences (34). Insomnia is often linked to amisulpride use in a psychiatric setting, where high doses of amisulpride (100-1200 mg/day, mean dose 670 mg/day) are used in the management of acute exacerbations of schizophrenia, while low doses of amisulpride (< 300 mg/day), applied in the treatment of negative symptoms of schizophrenia, showed similar incidence of AEs as compared to placebo (19). In the study of Kranke et al., the occurrence of insomnia was not found to be dose-dependent and first appeared > 48 hours after drug administration, exceeding 5-fold the half-life of intravenous amisulpride. Therefore, it

Table II. *Meta-analysis of overall adverse events in studies of amisulpride.*

Outcome	Studies	N	RR [95% CI]	*P* value	
Blood prolactin increased	1	689	8.97 [2.75, 29.30]	0.0003	
Any TEAE	5	3313	0.90 [0.84, 0.96]	0.0008	*P* value ≤ 0.05
Insomnia	1	215	2.13 [0.99, 4.57]	0.05	
Any life-threatening AE	5	3313	0.41 [0.13, 1.28]	0.13	
Pyrexia	1	215	4.72 [0.55, 40.87]	0.16	
Abdominal distension	1	689	1.63 [0.78, 3.40]	0.19	
Vomiting[a]	2	1849	0.80 [0.52, 1.24]	0.32	
Hypertension	1	215	1.99 [0.49, 8.06]	0.33	
Flatulence	4	2166	0.89 [0.69, 1.14]	0.35	
Constipation	5	3313	0.91 [0.71, 1.16]	0.43	
Nausea[a]	4	3098	0.93 [0.77, 1.13]	0.47	
Chills	1	1147	1.26 [0.66, 2.40]	0.49	
Pruritus	2	1391	0.86 [0.55, 1.35]	0.52	
Anemia	2	904	1.19 [0.7, 2.04]	0.52	*P* value > 0.05
Hyperglycemia	1	689	0.87 [0.56, 1.35]	0.52	
Leukocytosis	1	689	1.13 [0.66, 1.94]	0.66	
Dizziness	1	215	0.76 [0.21, 2.73]	0.68	
Any SAE	5	3313	0.95 [0.65, 1.39]	0.79	
Hypotension	3	2051	1.05 [0.69, 1.59]	0.82	
Pain	5	3313	1.01 [0.90, 1.13]	0.89	
Hypoproteinemia	1	689	1.04 [0.62, 1.74]	0.9	
Headache	3	1606	1.00 [0.50, 1.97]	0.99	
Hypocalcemia	1	689	1.00 [0.61, 1.62]	0.99	

[a]Excluding nausea and vomiting within 24 hours after the end of surgery or study drug administration.
RR, relative risk; CI, confidence interval; TEAE, treatment-emergent adverse event; AE, adverse event; SAE, severe adverse event.

remains unclear whether amisulpride contributes to sleep disorders after a single-dose administration (24, 33).

Although the use of dopamine antagonists is often associated with extrapyramidal symptoms, such as bradykinesia, tremor, akathisia, Parkinson-like rigidity, tardive dyskinesia as well as acute dystonia (24), none of these symptoms were observed in any of the trials included for the meta-analysis. This data is consistent with prior safety studies in psychiatric use, which showed that amisulpride did not cause more extrapyramidal side effects than the placebo (39).

Despite amisulpride being proven to be cardiovascular safe at doses ranging from 100 to 1200 mg/day (19), drug overdose with doses as high as 4-80 g is associated with QTc prolongation, bradycardia, hypotension and a risk of severe cardiac arrhythmias, including TdP (40, 41). The included studies on low-dose amisulpride did not report any severe cardiovascular AEs or any relevant QTc prolongation, however, only 3 studies (33-35) obtained the patients' electrocardiogram data postoperatively. Nevertheless, the effect of amisulpride on prolongation of the QT interval is dose-dependent. A thorough QT study of Taubel et al. also confirmed that intravenous amisulpride dose of 5 mg does not lead to prolongation of the QTc interval, while a 40-mg supratherapeutic dose was associated with a QTc prolongation of 23.4 ms from baseline; however, none of the subjects experienced an absolute QTcF value of > 500 ms (42).

The 2014 Consensus Guidelines for the management of PONV drew attention to combination therapy and multimodal approach based on patient's risk assessment for PONV (2). Different pharmacological classes of antiemetics were proven to show an additive effect on the PONV risk reduction when combined for the multimodal therapy (43). Since the FDA "black box" warning was issued in 2001, droperidol, which had been widely used as a first-line medication for the treatment of PONV, was withdrawn from the market in many countries due to safety concerns associated with the risk of QT prolongation and TdP, leaving a huge gap in PONV management (44, 45). Amisulpride, with its favorable pharmacokinetic profile and a low risk

of drug interactions, is a new, attractive pharmacological option for both prevention and treatment of PONV, especially in patients at a risk of cardiovascular complications (21). However, a recent systematic review of randomized controlled trials showed that low-dose droperidol (doses < 1 mg or < 15 μg/kg) was also effective and cardiovascular safe. The same study also reported potentially serious extrapyramidal side effects, which occurred even with low doses of droperidol (45). Therefore, the cost–benefit risk in patients with previously known QTc prolongation, or in patients at a risk of central AEs, should be considered while administering antiemetic therapy.

Amisulpride's antiemetic potential has also been investigated in chemotherapy-induced nausea and vomiting (CINV). A recent randomized, double-blind study of 318 patients receiving highly emetogenic chemotherapy for breast cancer showed that a single 10-mg oral dose of amisulpride was safe and effective at preventing CINV in its delayed phase (46).

A possible limitation of the available trials is that the majority of the patients were females (87.5%) undergoing general anesthesia, thus the results might not be generalizable to the whole surgical population; nevertheless, women are much more likely to experience PONV than men and so far, there is no convincing evidence that antiemetics effective in women do not work in men (5).

Another limitation is that all 5 studies only recruited adult patients, therefore the benefit and safety of amisulpride in the treatment of PONV in children remains unknown. Given the increased susceptibility of children to antidopaminergic drugs in general, this group of drugs is not the first choice in the pediatric population.

Furthermore, there are currently only few studies investigating amisulpride as prophylaxis and treatment for PONV. The effect estimates with 95% CIs were significant, but estimated effects reach areas of clinical nonrelevance (RR 0.8 to 1.25). Due to the imprecise result with the current number of studies and relatively low number of participants, we cannot be sure that amisulpride is favorable for any participant in any setting. To overcome this limitation, more participants have to be included in clinical studies with broader inclusion criteria. Furthermore, a comparison of amisulpride against well-known active interventions such as ondansetron or dexamethasone or combinations of such drugs (47) is necessary to put amisulpride's efficacy into context.

In conclusion, low-dose intravenous amisulpride is an effective antiemetic both for prevention as well as treatment of established PONV. It may be used as a monotherapy and as part of a multimodal antiemetic approach in combination with other antiemetics. Amisulpride, with its safety profile comparable to that of placebo, is a promising pharmacological option in the multimodal management of PONV. Further to this finding, it is the first time that a new antiemetic molecule is tested prior to approval for both the prevention and treatment of PONV. Further trials with active comparators must elucidate whether amisulpride's efficacy is comparable to those of other well-established interventions such as ondansetron or dexamethasone. Future trials may also help to define the best prophylactic combination against PONV and—in view of the relatively short half-life—whether a repetitive dosing in the postoperative course may further enhance antiemetic action. So far, clinical trials with amisulpride have not been performed in pediatric patients, which may prove to be a promising target population.

Disclosures

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An overview of intravenous amisulpride as a new therapeutic option for the prophylaxis and treatment of postoperative nausea and vomiting

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DRUG EVALUATION

An overview of intravenous amisulpride as a new therapeutic option for the prophylaxis and treatment of postoperative nausea and vomiting

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ABSTRACT

Introduction: Current therapies of postoperative nausea and vomiting (PONV) are based on a combination of antiemetics from different pharmacological classes. Dopamine receptor antagonists are one of the cornerstones of such multimodal antiemetic approach, with droperidol being the best studied representative of this group. Droperidol's use has significantly declined after the FDA's black-box warning in 2001 due to its QT-prolonging properties. Amisulpride is a promising antiemetic agent which could fill this gap.

Areas covered: In this review, the authors discuss the pharmacological profile as well as clinical safety and efficacy of intravenous amisulpride and its relevance in the management of PONV. The article is based on a Medline, ClinicalTrials.gov, and Cochrane Library search for studies on amisulpride conducted so far.

Expert opinion: Promising clinical results on Barhemsys®, an intravenous formulation of amisulpride, make it a potential future drug of choice from the dopamine receptor antagonist group, replacing droperidol after its safety concerns. Amisulpride's success on the market will mostly be determined by its cost-effectiveness and it will likely find a brighter use on the US-market, where the black-box warning led to droperidol's withdrawal, while in many European countries, droperidol is still being used as an antiemetic.

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Antiemetic; postoperative nausea and vomiting (PONV); amisulpride; benzamide; dopamine receptor antagonists; droperidol

1. Introduction

Postoperative nausea and vomiting (PONV), with its multifactorial etiology, remains a frequent complication linked to anesthesia and surgical procedures [1]. The general incidence of PONV ranges between 20% and 30% when balanced anesthesia techniques, including volatile anesthetics combined with opioids, are used without pharmacological prophylaxis. However, incidence can be as high as 80% in patients with multiple risk factors, which are either patient specific (female gender, history of PONV and/or motion sickness, nonsmoking status, younger age) or anesthesia related (use of volatile anesthetics, and/or nitrous oxide, duration of anesthesia and postoperative opioid use) [1–4]. PONV is characterized by physical signs but also distressing subjective symptoms of nausea or retching leading to patients' dissatisfaction associated with anesthesia [5,6]. Additionally, it may result in economic consequences of protracted postoperative stay in the recovery room, increased nursing time and, finally, readmission to the hospital following outpatient surgery [7]. In order to minimize the incidence of PONV, the 2014 Consensus Guidelines suggested a multimodal approach, consisting of both pharmacological and non-pharmacological (baseline risk reduction) interventions. Since none of the single antiemetic agents is fully effective at PONV management, a combination therapy of drugs acting on different receptors has been recommended. The main pharmacological options for PONV include corticosteroids, 5-hydroxytryptamine (5-HT3) receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, antihistamines (H1-antagonists), anticholinergics, as well as butyrophenones acting on dopamine-2 receptors [3]. As antagonists of each of these receptor systems appear to have similar efficacy and reduce the risk of PONV by approximately one-fourth (25%), the choice of appropriate agents is primarily a question of safety and side effects on the one hand and costs on the other hand [8]. Dopamine antagonist droperidol was a widely used cost-efficient antiemetic until 2001, when the US Food and Drug Administration (FDA) issued a black-box warning, raising safety concerns regarding the risk of QT interval prolongation (measured from the beginning of QRS complex to the end of the T-wave; QTc values ≥460 ms in women and ≥390 ms in men, adjusted to heart rate are considered prolonged) and serious cardiac arrhythmias, such as torsade de pointes [9–11]. Despite several authors summarizing existing evidence stating the safety of the drug in low doses (<2.5 mg) commonly used to prevent or treat PONV, droperidol is no longer a first-line antiemetic in many countries [12,13]. Haloperidol, a potential alternative to droperidol, has been shown to be an effective antiemetic at low doses (0.5 to 2 mg i.m. or i.v.). However, its use is also associated with a risk of QTc prolongation and its intravenous use as an antiemetic is not approved by the FDA [3]. As a consequence, the search for new agents targeting dopamine receptors with a favorable safety profile has recently been intensified [3]. In this context, several older drugs (typically antipsychotics) were reassessed with amisulpride emerging as the most interesting candidate.

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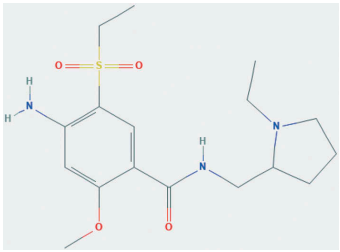
Article highlights

- Prophylaxis and treatment of postoperative nausea and vomiting requires a multimodal approach, including various antiemetics acting at different receptor sites.
- FDA's black box warning for droperidol due to QT-prolongation alienated anaesthesiologists and decreased the use of this potent dopamine2-antagonist.
- An aqueous solution of amisulpride (Barhemsys(R)), an alternative D2-antagonist with a superior safety profile will soon be available.
- Depending on economic considerations this drug has the potential to substitute droperidol within a multimodal antiemetic concept.

Box 1. Drug summary box.

Drug name	Amisulpride
Phase	Pre-registration
Indication	Postoperative nausea and vomiting
Pharmacology description	Dopamine D_2/D_3 receptor antagonist
Route of administration	intravenous
Chemical structure	
Pivotal trial(s)	NCT01510704 NCT01991860 NCT01991821 NCT02337062 NCT02449291 NCT02646566

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2. Overview of the market

Sulpiride, the oldest representative of the substituted benzamide group has been available on the market since 1967. Initially developed for the treatment of gastrointestinal disorders, it soon found its use as an antipsychotic and antidepressant [14]. Nowadays it is commonly prescribed in the treatment of tics as well as vertigo in many European countries; however, it has never been marketed in North America [14–16]. Its derivate, amisulpride, first introduced to the market in France over 30 years ago is currently approved in more than 50 countries worldwide (see Box 1). Indications for its oral use include both acute and chronic schizophrenia characterized by positive and/or negative symptoms [17,18]. In Italy, it is also approved for the treatment of dysthymia [19]. Recommended daily oral doses are ranging from 50 up to 1200 mg [18]. Since 2010, an extensive clinical research was carried out to determine amisulpride's efficacy in both mono- and combination therapy for PONV.

3. Introduction to the compound

Amisulpride (chemical name: (R, S)-4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-ethylsulfonyl-2- methoxybenzamide) is a substituted benzamide derivate belonging to the group of atypical antipsychotics [17,18]. It has been marketed as Solian ® since the 1980s (oral form of application) and recently available as Barhemsys®, a repurposed formula for intravenous injection.

4. Pharmacodynamics

Amisulpride is a highly selective dopamine D_2 (K_i = 2.8 nM), D_3 (K_i = 3.2 nM), and 5-HT7a serotonin receptor antagonist, which shows a low affinity for other dopamine and serotonin receptor subtypes as well as adrenergic, histamine, and cholinergic receptors [17–22]. Low doses show selectivity for presynaptic receptors, enhancing dopaminergic activity, whereas higher doses block postsynaptic dopamine D_2 and D_3 receptors, inhibiting the dopaminergic transmission [20]. These neurochemical features explain amisulpride's use at lower doses in the treatment of negative symptoms and at higher doses in the treatment of positive symptoms of schizophrenia [20,22]. The compound dosed as a racemate displays polypharmacy –

S-enantiomers target the dopamine D_2 and D_3 receptors and thus provide antipsychotic activity while the R-enantiomer shows a high affinity for the 5-HT7 receptor, which most likely contributes to antidepressant properties of amisulpride [21,23].

5. Pharmacokinetics and metabolism

Amisulpride's pharmacokinetic properties are characterized by rapid absorption with a biphasic profile, with the first plasma concentration peak occurring after 1 h (C_{max} = 42 ng/mL), followed by a second peak 4 h after oral administration (C_{max} = 56 ng/mL) with absolute bioavailability of 50% and a large volume of distribution (5.8 L/kg). Intravenous amisulpride is primarily excreted by the renal route in a largely unchanged form (50%), while the excretion of an oral dose is mainly to the fecal route (65%) than the renal one (35%) [24]. Hepatic metabolism is minimal and the two metabolites found in feces and urine are formed by oxidation and deethylation and are both inactive [25,26]. The terminal plasma elimination half-life ($t_{½}$) in healthy population is 7–8 h after intravenous and 12 h after the oral route of administration. Renal clearance (17–20 L/h in healthy volunteers) is reduced in patients with renal insufficiency and correlates linearly with the creatinine clearance reduction; therefore, in this population, the dose should be decreased [18,27,28]. Minimal plasma protein binding (17%), low metabolism, and no inhibition of the cytochrome CYP 450 system's activity determine amisulpride's low potential for drug interactions [29].

6. Clinical efficacy

Intravenous amisulpride (1 mg, 5 mg, and 20 mg single doses) was first tested for PONV monoprophylaxis in a randomized, double-blind, dose-finding Phase II study of 215 surgical patients with a moderate to high risk of PONV (see Table 1 for a comprehensive summary of available clinical trials). Significant reduction of PONV incidence in the 24-h postoperative period was observed in the 5 mg group (40%, 90% CI: 28–53%, p = 0.006) as compared to placebo (69%, 90% CI: 57-79%), which was found to be the optimal dose for preventing PONV with a safety profile similar to placebo [30].

Gan et al. then examined a single 5-mg dose in two concurrent Phase III trials (n = 689) held in Europe and the United States in patients with a moderate to high risk of PONV; the pooled data of both those studies confirmed the previous efficacy and safety results [31].

In 2018, Kranke et al. published a trial that investigated a 5-mg dose in combination with an antiemetic of a different pharmacological class (most commonly dexamethasone or ondansetron) in patients (n = 1147) with a high risk for PONV. The incidence of PONV or rescue medication use 24 h after surgery was significantly lower in the amisulpride group (p < 0.001). Again, adverse events did not significantly differ between the two groups [32].

Candiotti et al. studied amisulpride for the treatment of established PONV in patients (n = 560) with a low to moderate risk profile who had not received any prior antiemetic prophylaxis. Both 5 mg (p = 0.016) and 10 mg (p = 0.016) amisulpride doses were superior to placebo in the 24-h period after intravenous administration with a comparable incidence of adverse events in all three groups [33].

The most recent randomized, placebo-controlled, multicenter Phase III trial of Habib et al. evaluated amisulpride's efficacy in the treatment of established PONV after failed prophylaxis. Seven hundred and two patients with moderate to high risk of PONV were randomized to receive a single 5 mg, 10 mg, or placebo intravenous amisulpride dose. Patients who received the 10-mg dose (p = 0.006) experienced significantly fewer emetic episodes than the placebo group in the 24 h following the drug administration; however, no significant benefit was shown for the 5-mg dose (p = 0.109). The safety profile was comparable between all three groups [34].

7. Safety and tolerability

Intravenous amisulpride, administered at doses ranging from 5 to 20 mg a day in the management of PONV, was associated with a lower risk of side effects than the placebo, with insomnia and serum prolactin level elevation being the only significantly more frequent treatment-emergent adverse events in the previously reviewed studies [35]. Insomnia first appeared over 48 h after intervention, which is significantly longer than the half-life of intravenous amisulpride [30], while the prolactin-elevating effect was small and did not exceed the norm for non-pregnant women [31]. Therefore, both of these adverse events appear to be of no clinical significance with a single-dose treatment. Notably, toxicities usually associated with dopamine antagonists, including extrapyramidal symptoms and cardiac arrhythmias, were not observed in any of the studies. This data is consistent with the experience with intravenous amisulpride in the delayed phase of chemotherapy-induced nausea and vomiting (CINV) [36,37].

Cardiovascular safety of intravenous amisulpride was also been evaluated in the study of Taubel et al., where a 5-mg therapeutic dose for PONV had no significant effect on the QTc interval prolongation. Higher supratherapeutic doses of 40 mg led to QTc prolongation of 23.4 ms from baseline; however, the absolute QTcF values >500 ms were never exceeded [38]. Therefore, the prolongation of QTc interval appears to be dose-dependent, a phenomenon also observed in CINV trials of intravenous amisulpride [36,37]. The increase in QTc prolongation from baseline is still 3- and 5-fold lower than with 4-mg ondansetron and 1-mg droperidol, respectively [39].

This benign safety profile of intravenous amisulpride is consistent with the studies in the psychiatric population where much higher oral doses (50–800 mg/day) are often administered over prolonged periods of time. At low doses (≤300 mg/day) the incidence of side effects is comparable to placebo [17]. Higher doses used for acute treatment of schizophrenia were associated with significantly elevated prolactin levels with the incidence of extrapyramidal side effects similar to placebo [40].

8. Regulatory affairs

In 2010, a repurposed intravenous formula of amisulpride was patented. A clinical study program was started under the investigational drug name APD421 for the indication of prophylaxis and treatment of PONV and CINV [41]. The findings have undergone a systematic study program that received a positive evaluation by the FDA. However, in May 2019 the FDA identified deficiencies of the contract manufacturer of amisulpride and thus postponed approval of the drug Barhemsys®. In July 2019, Acacia Pharma Group announced to resubmit the NDA designating a new supplier of amisulpride. In September 2019, the FDA set a PDUFA date for a decision on Barhemsys® for 26 February 2020.

9. Conclusion

Intravenous amisulpride emerges as a new and effective antiemetic with an overall safety profile comparable to placebo. Doses as low as 5 mg used in mono- and combination therapy effectively prevent PONV within the 24-h postoperative period. Both 5-mg and 10-mg doses were effective in the treatment of established PONV in patients with no prior prophylaxis; however, only the 10-mg dose was efficient at treating PONV after failed prophylaxis. The drug shows no relevant increase in QT time and thus is superior to other antiemetics from the group of dopamine receptor antagonists. Side effects of low doses of amisulpride tested for PONV are infrequent and benign. In the light of these encouraging safety issues, the drug has the potential to substitute other D2-antagonists. However, the final price must be outweighed against older drugs like droperidol.

Table 1. Summarizes studies on intravenous amisulpride for PONV with their characteristics as well as safety and efficacy results.

Study	Phase	Number of patients	PONV r	Dose	Comparator	Purpose of the study	Primary endpoint	Complete response	Side effects
Habib 2019 [34]	III	702	Moderate-to-high risk	Single 5mg or 10 mg amisulpride iv	Placebo	Efficacy of amisulpride as rescue treatment of PONV in patients after failed prophylaxis	No emesis or rescue medication use in the period 30 min-24 hours after study drug treatment	5 mg 33.8% (95% CI, 27.7–39.8; p = 0.219); 10 mg 41.7% (95% CI, 35.4–48.1; p = 0.006), placebo 28.5% (95% CI, 22.7–34.3)	TEAE comparable between amisulpride and placebo groups
Candiotti 2019 [33]	III	560	Low-to-moderate risk	Single 5 mg or 10 mg amisulpride iv	Placebo	Efficacy of amisulpride in treatment of established PONV in patients with no prior prophylaxis	No emesis or rescue medication use in the period 30 min-24 hours after study drug treatment	5 mg 31.4% (95%CI, 24.83–38; p = 0.016); 10 mg 31.4% (95% CI, 24.75–38.02; p = 0.016); placebo 21.5%(95% CI; 15.56–27.54)	Fewer TEAEs in both 5 mg and 10 mg groups than placebo; no extrapyramidal or cardiac side effects reported
Kranke 2018 [32]	III	1147	3-4 Apfel score risk factors	Single 5 mg amisulpride iv + standard antiemetic	Placebo + standard antiemetic	Efficacy of amisulpride in combination with an emetic from another class in prevention of PONV	No emesis or rescue medication use in the 24-hour postoperative period	5 mg 57.7% (95% CI, 53.6–61.7; p < 0.001); placebo 46.6% (95% CI, 42.5–50.7)	Fewer TEAE in the amisulpride group; no extrapyramidal or cardiac side effects reported; QTc change from baseline similar between two groups
Gan 2016* [31]	III	626	≥2 Apfel score risk factors	Single 5 mg amisulpride iv	Placebo	Efficacy of amisulpride in prevention of PONV	No emesis or rescue medication use in the 24-hour postoperative period	5 mg 52.1% (95% CI, 46.4–57.7; p = 0.005)	TEAE comparable between amisulpride and placebo group; significantly increased prolactin levels in amisulpride group; no difference it QT prolongation, no extrapyramidal side effects reported
Kranke 2013 [30]	II	215	≥2 Apfel score risk factors	Single 5 mg, 10 mg or 20 mg amisulpride iv	Placebo	Efficacy of amisulpride in prevention of PONV, Dose-Finding Study	PONV (vomiting/retching or antiemetic rescue) in the 24-hour postoperative period	1 mg 48% (90% CI, 37–60; p = 0.048); 5 mg 40% (90% CI, 28–53; p = 0.006); 20 mg 57% (90% CI, 44–68%; p > 0.1), placebo 69% (90%CI, 57–79)	Incidence of TEAE similar across all study groups, no extrapyramidal or cardiac side effects reported

*Efficacy of intravenous amisulpride in PONV prevention. See reference #31.

10. Expert opinion

Current therapies for patients with moderate to high risk of PONV are based on a multimodal approach, including combination therapy with different pharmacological classes of antiemetics in order to achieve optimal effects [3]. One class of antiemetics has lost relevance since a well-established, effective, and frequently used representative of this group, droperidol, was labeled with a black-box warning in 2001. Since then, the use of droperidol has significantly declined and thus created the need for other antiemetics acting on the dopamine receptor [42]. Another representative of this class, haloperidol, also received a black-box warning for its QTc prolonging properties in 2007 [3]. One other potential candidate, metoclopramide, also an intensively investigated antiemetic, lost attractiveness when the European Medicines Agency recommended in 2013 that higher doses needed for the prophylaxis of PONV should no longer be used as first-line therapy [43]. Other older dopamine receptor antagonists may be effective but lack systematic investigations on potential side effects [44]. Amisulpride has the potential to fill this gap. Results from a clinical study program revealed promising results. Since the antiemetic properties of the drug known for its D_2 /D_3 antagonistic effects are not surprising, it is mainly the low incidence of side effects that make amisulpride an interesting innovation for the anesthesia community. Not only safety issues, like the minimal prolongation of QT-time, but also low incidences of side effects make amisulpride a valuable addition for a multimodal antiemetic approach. The new drug, Barhemsys®, will come as a 5 mg i.v. formulation for the prophylaxis and treatment of ongoing nausea and vomiting. While amisulpride is more likely to find a brighter use as a new dopamine receptor antagonist on the US market, its role as an antiemetic in Europe will be limited by droperidol's availability in many countries. In the US, the use of droperidol has decreased since 2001 but this was not only caused by safety concerns. The major reason for the declined use of droperidol was its lack of availability since the original manufacturer voluntarily withdrew droperidol from the market. During this period droperidol was not substituted by other dopamine receptor antagonists. Instead, the use of dexamethasone and 5-HT3 antagonists gained popularity, and many anesthesiologists are not familiar with droperidol anymore. As of today, droperidol's cost as a generic substance on the European market is not relevant; however, amisulpride, as a newly developed competitor, will lack cost efficiency. Competition also comes from aprepitant, an NK1-antagonist that is now available as a generic drug for antineoplastic chemotherapy and may soon be available for the PONV indication as well. Despite several pharmacokinetic interactions due to its metabolism via the CYP3A4 pathway, aprepitant is a safe drug with a low incidence of side effects [45]. It also has the potential to complement the pharmacologic armamentarium against PONV. In the view of these emerging possibilities, blockade of the dopamine receptors still remains a cornerstone of antiemetic treatment. Amisulpride has the potential to become the drug of choice in this pharmacologic group and to substitute other dopamine receptor antagonists, like droperidol.

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8.2 *Curriculum vitae*

Der Lebenslauf enthält persönliche Daten und wurde deshalb vor Drucklegung entfernt.

8.3 *List of academic teachers*

My academic teachers at the Medical University of Silesia were:

Prof. J. Baron, Prof. P. Bażowski, Prof. J. Bohosiewicz, Dr. W. Chociłowski, Dr. C. Chowaniec, Prof. J. Chudek, Prof. L. Cierpka, Dr. I. Duda, Prof. J. Duława, Dr. J. Durmała, Dr. T. Francuz, Prof. A. Franek, Prof. J. Gielecki, Prof. J. Gmiński, Prof. M. Hartleb, Prof. M. Kamiński, Prof. M. Kawecki, Prof. Z Kondera-Anasz, Prof. I. Krupka-Matuszczyk, Dr. H. Kulik, Prof. D. Kusz, Prof. J. Lewin-Kowalik, Dr. J. Litwiński, Prof. W. Lukas, Prof. I. Niedzielska, Prof. E. Małecka-Tendera, Prof. J. Markowski, Prof. W. Mazur, Prof. G. Martirossian, Prof. Maruniak-Chudek, Prof. B. Okopień, Prof. G. Opala, Dr. K. Pawlicki, Prof. W. Pierzchała, Prof. W. Romaniuk, Prof. A. Sieroń, MSc S. Sobczak, Prof. L. Szydłowski, Prof. M. Tendera, Dr. A. Trzecieniecka-Green, R. Wiaderkiewicz, Prof. A. Wiącek, Prof. A. Witek, Prof. J. Wojnar, Prof. H. Woś, Prof. J. Zejda, Prof. K. Ziaja.

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8.5 *Ehrenwörtliche Erklärung*

Die ehrenwörtliche Erklärung wurde vor Drucklegung entfernt.